Special Issue title: **LIVING PAPER: COVIPENDIUM**

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LIVING PAPER: COVIPENDIUM

The place of the Covipendium within the growing amount of Covid-19 literature

At the start of the Covid-19 pandemic, in February 2020, I was lucky enough to attend the World Health Organization meeting where about 300 experts from around the world attempted to coordinate the required research efforts (https://www.who.int/publications/m/item/a-coordinated-global-research-roadmap). The priorities were twofold. First, there was a need to better understand the virus and its transmission, so as to limit the spread of the pandemic, and to rapidly make sure that those suffering from a severe form of the disease receive optimal care. The second goal was to allow for the development of diagnostic tools, therapeutics and vaccines.

My main recollection from this conference is the words of Dr Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization. They were not just pleasantries, but instead urged us to collaborate, to be transparent, to work hard. This speech made us all vibrate with incredible energy, with the same deep determination to shake up our ways of working, and to do better, much better, much more, for the benefit of humanity.

In a funny coincidence, since the end of 2018 I had been busy writing a document on pandemic risks and possible control mechanisms. So it is no surprise that I felt my mission was to communicate about this new virus. Given my experience during the Ebola and Zika epidemics, it seemed obvious to me that a living document format, with frequent updates, would be necessary. I also understood that scientists would benefit greatly from an overview of the subject that would be as complete as possible. I figured out a document that was both structured and very detailed, using internet links, a bit like a Wikipedia page. I had thought of calling it Covipedia. To give it a more medical connotation, it was finally named Covipendium.

For this Covipendium to flourish, it was necessary to showcase it online, as a means of disseminating the document. At the time of the World Health Organization meeting in February, the topic of scientific information was at the centre of some passionate debates. Several institutions wanted to take leadership in the field, each with their own methodology (see for example https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov). They did not consider my ideas, even though several experts were very enthusiastic about them. Finally, a team at KU Leuven in Belgium, together with the Transdisciplinary Insights journal, offered a home for the Covipendium. I would like to express my gratitude to this wonderful team. With their support, the first version of the document came online on 5 March

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2020. I also like to thank Zenodo, which provides a publication system perfectly suited to the concept of a living document. This platform helped disseminate the Covipendium even more widely (https://zenodo.org/record/4273202#.X_B0ydhKg2w; 9,750 views as of 2 January 2021).

Other living reviews on Covid-19 were of course created in parallel to our initiative. Kamps and Hoffman developed the Covid Reference, which has now reached its fifth edition (https://covidreference.com/). But each publisher defines its project with a specific objective. The Covid Reference provides a good analysis of available data, a perfect format, and a traditional table of contents (including the usual elements of a scientific review paper on a disease). By contrast, the Covipendium focused on rapid dissemination of information (with weekly updates) and the breadth of the overview it provided of the virus, the disease, and its control. Over the weeks, it became increasingly important to us to broaden our readers' understanding of the pandemic: to present the psychiatric consequences of containment measures, the problem of the shortage of surgical masks, ethical problems encountered by health care professionals and so on. We would have liked to broaden the scope of our review even further, to shed light on economic issues, the social aspects of the pandemic, and the role played by the media, as well as to talk about resilience.

On 19 October 2020, the London School of Hygiene and Tropical Medicine table (https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/) identified 248 vaccine candidates under evaluation. So much effort, and money, spent for the same purpose. I wonder how many scientists involved in this research took the time to consider the overall framework and honestly assess whether their work was the best contribution they could make to the needs of the world, with the best cost–benefit ratio. For instance, considering the level of hesitation associated with the new vaccines, don't we need more research into the risk factors of serious adverse reactions? And given that outbreaks of other new viral diseases remain a threat, should we not be paying more attention to non-specific stimulation of host resistance? Would we not be able to better target disease control efforts if the risk factors of severe forms of the disease were more precisely identified?

We updated the Covipendium almost every week until 20 October 2020. Why did we stop the project then? The document was created at the very beginning of the pandemic, at a time when no review paper was available, and relevant information was lacking, not only to guide public health decisions but also to support the development of diagnostic tests, vaccines and therapies. The document thus filled a gap; it provided a resource that was considered very useful, at least by the many readers who contacted us. Over a few months, however, the needs in terms of information on Covid-19 evolved. Case reports from China were no longer of interest to anyone at a time when large cohorts and randomised controlled trials were providing much stronger data. We tried to keep the document alive as long as possible, gradually replacing some sections that had become obsolete and creating new chapters that we viewed as important. But the workload required to ensure the Covipendium maintained a sufficient level of quality quickly exceeded the capabilities of our small team. It was best we put an end to the project.

This publication results from the last Covipendium update, on 20 October 2020. It addresses most of the comments by Guido Vanham, the expert reviewer, to whom we are very grateful for his insightful communications.

The Covipendium would not have been possible without several co-authors (Valerie Vandeweerd, Rein Verbeke, Anne Laudisoit, Tristan Reid, Emma Hobbs, Laure Wynants and Diane Van der Vliet). I pay tribute to their enthusiasm, energy and competencies. I would have liked to see more people like them join the adventure. But how many experts on a given subject are willing to volunteer for the somewhat boring activity of literature monitoring and writing? Especially in a period as intense for them as the one we were going through? I therefore wish to thank wholeheartedly those who built the Covipendium over these few months.

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Comments on the Covipendium

The present Covipendium offers a comprehensive overview of the scientific literature about SARS-CoV-2 and Covid-19 during the first 10 months of 2020. It relies mostly on published papers, including pre-prints, but this traditional source has been complemented by references to very interesting websites that collect and regularly update epidemiological data, data on therapeutics and vaccines, etc. In some instances, reference is also made to press releases, for example when formal publications on potentially ground-breaking findings are still lacking. This "inclusive" approach is acceptable for this rapidly evolving field, but a word of caution should perhaps be expressed, since only part of the information is peer-reviewed.

This enormous literature has been nicely organised into chapters and paragraphs in such a way that a student who is new to and naive about the field can start on page 1 and gradually acquire the necessary knowledge to be able to read and understand the most recent papers at the end. On the other hand, more established scholars, scientists and medical practitioners, who often lack the time and energy to follow and read every new paper, can rapidly check their field of interest and fill the gaps in their knowledge. Clearly, while most useful at this very moment (the end of the first year of the Covid era), this compendium will remain a source of information for all those who are interested to learn about the concepts and findings during the early months of this pandemic.

Most chapters provide a short introduction, followed by an overview of the relevant papers, either just as bullet points with references or as one or two sentences with the main findings. At the end of each paragraph, a brief discussion of systematic overviews of the topic is usually offered. In a few chapters, the authors have gone a step further by writing their own review. Thus, the chapters on clinical and epidemiological aspects take more the form of a list and eclectic summary of the literature. Similarly, the chapters on therapeutics and vaccines remain very factual, but are very useful and comprehensive. Conversely, the chapters on animal models and human-to-animal transmission provide more of an insightful review. All of these approaches are fine, since they stick to the primary goal of this compendium: to give as complete an overview as possible of the state-of-the-art up to October 2020.

Here are some minor criticisms:

– The section on epidemiology is somewhat superficial and does not sufficiently stress the variability in various parts of the world. We add a potentially useful reference in this respect.
– The definition of "case" is only given on p. 63, whereas the "case fatality rate" is already discussed on p. 52. This part is difficult to follow, as the distinction between the "case fatality rate" (i.e. according to the definition of a "case") is confused

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with the “infection fatality rate” (i.e. according to all infections, as determined by mass testing and/or sero-surveillance).

– The chapters on “Social Interventions” and “Implications of the Covid-19 Pandemic” are rather short and do not cover the vast literature that has appeared in those fields. However, this is probably beyond the scope of this compendium, which is more focused on biomedical aspects. This could be clarified.

All in all, this has been an enormous effort with a very fruitful and useful result. This unique resource should be made widely available and visible to interested biomedical scientists, in order to support their orientation in the rapidly evolving “Covid-ology”.

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Information available to support the development of medical countermeasures and interventions against COVID-19

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For navigation through the various sections, please click on the headings of the table of contents and follow the links marked in blue in the document.

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Contents

List of abbreviations

AAK1	AP2-associated protein kinase 1
ACE2	angiotensin-converting enzyme 2
AGM	African Green Monkey
AI	artificial intelligence
ALB	albumin
ALT	alanine aminotransferase
AMPs	Antimicrobial peptides
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AT2	type II alveolar cells
BMI	body mass index
CDCs	cardiosphere-derived cells
CI	confidence interval
CNS	central nervous system
CoV	coronavirus
CPK	creatine phosphokinase
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computed tomography
DPC	days post challenge
ELISA	enzyme-linked immunosorbent serologic assay
GISAID	Global Initiative on Sharing All Influenza Data
HCW	health care worker
HIV	human immunodeficiency virus
IC50	half maximal inhibitory concentration
IFN	interferon
ISG	IFN-stimulated genes
mAb	monoclonal antibody
MERS	Middle East respiratory syndrome
MHV	murine hepatitis virus
MOI	multiplicity of infection
MSCs	mesenchymal stem cells
N	nucleocapsid
NAb	neutralizing antibody
NCIP	novel coronavirus-infected pneumonia
NK	natural killer
N.R.	not reported
PAD	Primary Antibody Deficiencies
PCR	polymerase chain reaction
PD	pharmacodynamic
pfu	plaque-forming unit
PK	pharmacokinetic
PPE	personal protective equipment
PRNT	plaque-reduction neutralization test
R&D	research and development
RAS	renin-angiotensin system
RBD	receptor-binding domain
RH	relative humidity
RT-PCR	real-time polymerase chain reaction
S	spike
SAA	serum amyloid A
SARS	severe acute respiratory syndrome
VNT	virus neutralization test
WHO	World Health Organization

Foreword

The COVIPENDIUM was an initiative of the Institute for the Future of the Rega Institute (KU Leuven, Belgium). It was created at the start of the COVID-19 epidemic in February 2020, as a living paper on the new coronavirus disease. The project aimed at providing a structured compilation of available scientific data about the virus, the disease and its control. Its objective was to help scientists identify the most relevant publications on COVID-19 in the wealth of information published every day.

The COVIPENDIUM was also expected to foster a global understanding of disease control and stimulate transdisciplinary initiatives. To this end, special attention was given to the development of a broad table of contents, addressing the widest spectrum of publications related to the disease and its consequences.

This living paper has been updated on a weekly basis until mid-September. Due to the huge amount of information published by that time, it had become more and more difficult to maintain the COVIPENDIUM up-to-date. The authors therefore decided to put an end to this initiative. The latest version of the document, dated October 20, is meant to provide to the reader the information gathered over the 9-month period of the project, and illustrate the benefits of organizing available information using both a living paper approach and a wide multi-disciplinary dimension.

Introduction

Coronaviruses are common human pathogens, causing generally-mild acute respiratory illnesses known as the common cold (Wu Euro Surv 2020, see ***below***). Prior to December 2019 when clusters of pneumonia cases with unknown aetiology were detected in Wuhan, China, only two additional strains of coronaviruses had caused outbreaks of severe acute respiratory disease in humans: the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). On 9 January 2020, a novel coronavirus, 2019-nCoV (temporary name), was officially identified as the cause of an outbreak of viral pneumonia in Wuhan (https://www.who.int/china/news/detail/09-01-2020-who-statement-regarding-cluster-of-pneumonia-cases-in-wuhan-china). The timeline of medical and scientific events up to June 2020 has been described by Carvalho (Nat Med 2020, see ***below***).

The virus spread rapidly within China, and an increasing number of cases appeared in other countries. On January 30th 2020, the outbreak was said to constitute a Public Health Emergency of International Concern https://www.who.int/publications/m/item/covid-19-public-health-emergency-of-international-concern-(pheic)-global-research-and-innovation-forum). The disease was named COVID-19 by WHO on February 11 2020 (https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020), and the virus named SARS-CoV-2 by the International Committee on Virus Taxonomy on the same day (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses Nat Microbiol 2020, see ***below***). Subsequently, a group of virologists in China suggested renaming SARS-CoV-2 as human coronavirus 2019 (HCoV-19), considering that such a name would distinguish the virus from SARS-CoV and keep it consistent with the WHO name of the disease it causes, COVID-19 (Jiang Lancet 2020, see ***below***). Virus naming long remained controversial (Voice from China Chin Med J 2020, see ***below***) and in the scientific literature, the virus can be referred to by these different names, even though Wu, Ho et al. (Lancet 2020, see ***below***) suggested keeping SARS-CoV-2 as its name.

On March 11 2020, WHO characterised COVID-19 as a pandemic (https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020).

Despite the wide implementation of a number of public health measures, the epidemic continued to progress in the months that followed this announcement. As of October 20 2020, 12:00 CET, according to WHO, a total of 40 114 293

cases has been confirmed globally, including 1 114 692 deaths. The vast majority of the cases has been reported by other countries than China (e.g. U.S.A. 8 065 615, India 7 597 063, Brazil 5 235 34, Russian Federation 1 415 316, vs. China 91 546).

The virus

Coronaviruses

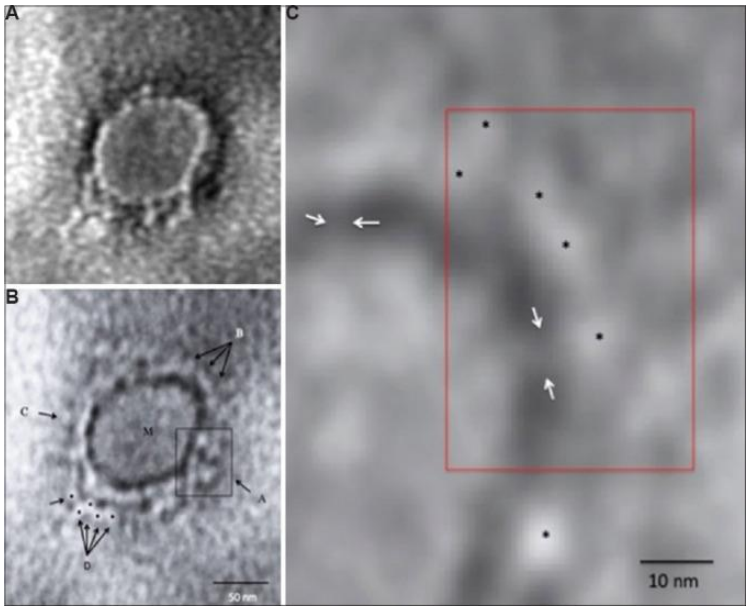
Coronaviruses (CoVs) are enveloped, positive-sense, single-stranded RNA viruses that belong to the subfamily Coronavirinae, family Coronavirdiae, order Nidovirales. The virion has a nucleocapsid composed of genomic RNA and phosphorylated nucleocapsid (N) protein, which is buried inside phospholipid bilayers and covered by spike proteins (Li J Med Virol 2020, see ***below***). The membrane (M) protein (a type III transmembrane glycoprotein) and the envelope (E) protein are located among the spike (S) proteins in the virus envelope. CoVs were given their name based on a characteristic crown-like appearance.

There are four genera of CoVs, namely, Alphacoronavirus (αCoV), Betacoronavirus (βCoV), Deltacoronavirus (δCoV), and Gammacoronavirus (γCoV) (Chan Em Micr Inf 2020, see ***below***). Evolutionary analyses have shown that bats and rodents are the gene sources of most αCoVs and βCoVs, while avian species are the gene sources of most δCoVs and γCoVs. CoVs have repeatedly crossed species barriers and some have emerged as important human pathogens.

The genomic RNA is used as template to directly translate polyprotein (pp) 1a/1ab, which encodes non-structural proteins to form the replication-transcription complex (RTC) in a double-membrane vesicles (Chen J Med Vir 2020, see ***below***). Subsequently, a nested set of subgenomic RNAs are synthesized by the RTC in a manner of discontinuous transcription. The first ORFs (ORF1a/b), about two-third of the whole genome length, encode 16 non-structural proteins (nsp1-16). Other ORFs on the one-third of the genome near the 3'-terminus encodes the main structural proteins: S, M, E, and N proteins. Besides these four main structural proteins, CoVs encode special structural and accessory proteins. All the structural and accessory proteins are translated from the subgenomic RNAs of CoVs.

Prasad (Ind J Med Res 2020, see ***below***) presented electron microscopy images of the virus (***Figure 1***). The images revealed the presence of stalk-like projections ending in round peplomeric structures typical of a coronavirus particle.

Figure 1 Transmission electron microscopy imaging of SARS-CoV-2 (from Prasad Ind J Med Res 2020)



Transmission electron microscopy imaging of COVID-19. (A) A representative negative-stained COVID-19 particle showing morphodiagnostic features of family Coronaviridae. (B) Defocussed image of the same particle resolving the virus envelope glycoprotein morphology in finer details. The boxed area A shows a tetramer-like aggregate of four distinct peplomers, arrows shown by B show a more orthodox morphology of coronavirus surface projections. M indicates the matrix of the virus particle. C shows a distinct 'peplomer head' with negative stain silhouette. The area D is interesting as possible linear projections could be imaged. Five distinct peplomers could be imaged as shown by the arrows. (C) A highly magnified processed image for pixel corrections shows a distinct evidence of direct 'stalk' connecting the peplomer to the virion surface. The peplomers are shown with asterisk and the stalk with an arrow. Magnification bars are built into the micrographs.

SARS-CoV-2 is a betacoronavirus

On January 3, 2020, the first complete genome of the novel β genus coronaviruses (2019-nCoV, subsequently named SARS-CoV-2) was identified in samples of bronchoalveolar lavage fluid from a patient from Wuhan (http://weekly.chinacdc.cn/en/article/id/a3907201-f64f-4154-a19e-4253b453d10c and Wu Nature 2020, see ***below***). A viral genome sequence was released via the community online resource virological.org on 10 January (Wuhan-Hu-1, GenBank accession number MN908947 (http://virological.org/t/novel-2019-coronavirus-genome/319). Additional sequences were rapidly obtained by other groups and complete genomes were submitted to GISAID (see for instance, Zhu New Engl J Med 2020 ***below***).

SARS-CoV-2 falls into the genus *betacoronavirus*, which includes CoVs discovered in humans, bats, and other wild animals (SARS-CoV, bat SARS-like CoV, and others). As illustrated in ***Table 1*** below, additional studies, based on subsequent virus isolates, confirmed that the virus is phylogenetically closest to bat SARS-like CoV (SL-ZC45 and SL-CoVZXC21).

Table 1 SARS-CoV-2 sequence similarity with other coronaviruses

% similarity with				reference
SARS	MERS	bat SARS-like CoV*	BatCoV RaTG13	
N.R.	N.R.	89.1%	N.R.	Wu Nature 2020, see ***below***
79.0%	51.8%	87.6-87.7%	N.R.	Ren Chinese Med J 2020, see ***below***
82%	N.R.	89%	N.R.	Jiang Em Micr Inf 2020, see ***below***
82%	N.R.	89%	N.R.	Chan Em Micr Inf 2020, see ***below***
79%	50%	88%	N.R.	Lu Lancet 2020, see ***below***
N.R.	N.R.	N.R.	96.3%	Paraskevis Infect Genet Evol 2020, see ***below***
<80%	N.R.	N.R.	96.2%	Zhou Nature 2020, see ***below***
79.7%	N.R.	87.9%	N.R.	Chen Em Micr Inf 2020, see ***below***

** bat-SL-CoV-ZC45 and/or bat-SL-CoV-ZXC21*

The observation that SARS-CoV-2 isolates have a single intact open reading frame gene 8 is a further indicator of bat-origin CoVs. In addition, although closely related to BatCoV RaTG13 sequence throughout the genome (sequence similarity 96.3%), SARS-CoV-2 shows discordant clustering with the Bat_SARS-like coronavirus sequences (Paraskevis Infect Genet Evol 2020, see ***below;*** Lu Lancet 2020, see ***below***). Specifically, in the 5'-part spanning the first 11,498 nucleotides and the last 3'-part spanning 24,341-30,696 positions, SARS-CoV-2 and RaTG13 formed a single cluster with Bat_SARS-like coronavirus sequences, whereas in the middle region spanning the 3'-end of ORF1a, the ORF1b and almost half of the spike regions, SARS-CoV-2 and RaTG13 grouped in a separate distant lineage within the **sarbecovirus** branch. Consequently, the levels of genetic similarity between SARS-CoV-2 and RaTG13 suggest that the latter does not provide the exact variant that caused the outbreak in humans, but the hypothesis that SARS-CoV-2 has originated from bats is very likely.

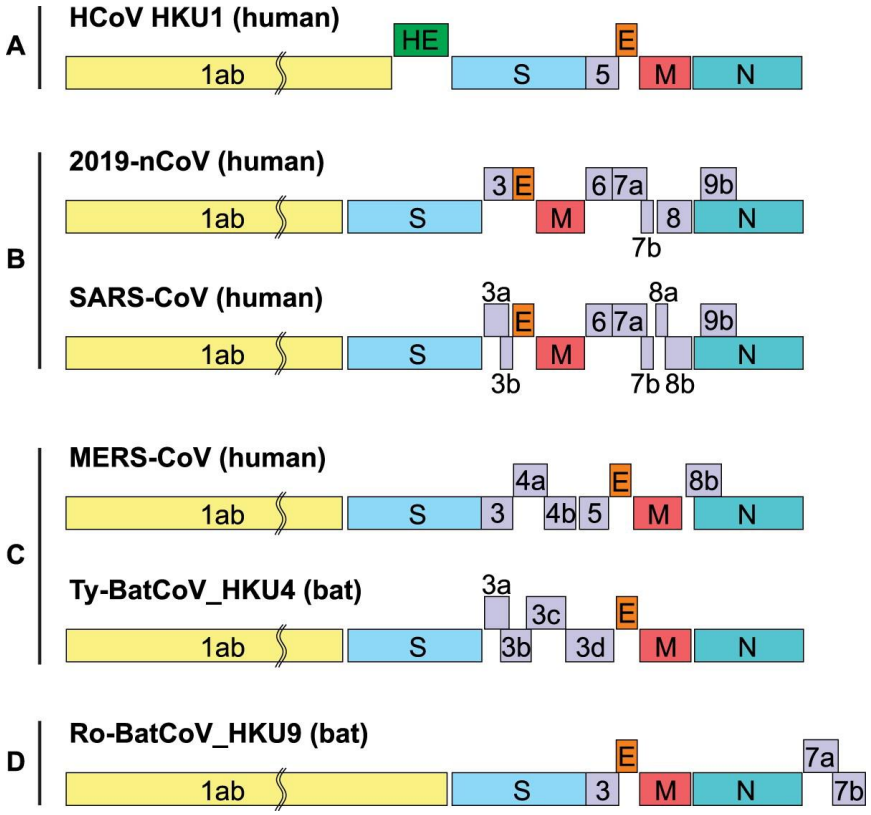
Genome structure

Similar to other βCoVs, the SARS-CoV-2 genome contains two flanking untranslated regions and a single long open reading frame encoding a polyprotein (Chan Em Micr Inf 2020, see ***below)***. The SARS-CoV-2 genome is arranged in the

order of 5'-replicase (orf1/ab)-structural proteins [S-E-M-N]−3' and lacks the hemagglutinin-esterase gene which is characteristically found in lineage A β-CoVs, as illustrated in ***Figure 2***.

The genome of SARS-CoV-2 encodes four major structural proteins [spike (S), envelope (E), membrane (M), and nucleocapsid (N)], approximately 16 nonstructural proteins (nsp1–16), and five to eight accessory proteins (Jiang Trends Imm 2020, see ***below***). Among them, the S protein plays an essential role in viral attachment, fusion, entry, and transmission. It comprises an N-terminal S1 subunit responsible for virus-receptor binding and a C-terminal S2 subunit responsible for virus-cell membrane fusion. The S1 subunit contains a signal peptide, followed by an N-terminal domain (NTD) and receptor-binding domain (RBD), while the S2 subunit contains conserved fusion peptide, heptad repeat 1 and 2, transmembrane domain, and cytoplasmic domain.

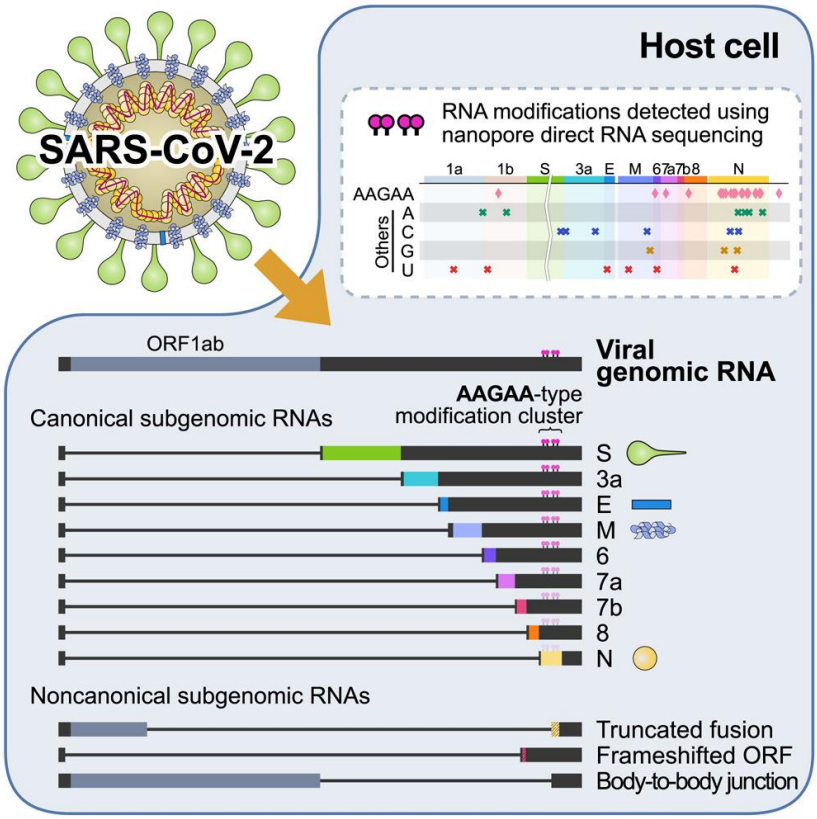
Figure 2 Genome organization of the SARS-CoV-2 genome compared to other betacoronaviruses (from Chan Em Micr Inf 2020)



Remarkably, orf3b encodes a completely novel short protein. Furthermore, new orf8 likely encodes a secreted protein with an alpha-helix, following with a beta-sheet(s) containing six strands.

Using direct RNA sequencing and sequencing-by-synthesis methods, Kim (Cell 2020, see ***below***) provided a high-resolution map of the SARS-CoV-2 transcriptome and epitranscriptome. In addition to viral genomic RNA and 9 canonical subgenomic RNAs, SARS-CoV-2 produces transcripts encoding unknown ORFs with fusion, deletion, and/or frameshift (***Figure 3***). The authors also found at least 41 RNA modification sites on viral transcripts, with the most frequent motif, AAGAA.

Figure 3 Graphical presentation of the data by Kim (Cell 2020)



Origin of the virus

Phylogenetic and likelihood-mapping analyses of 12 genome sequences of the virus with known sampling date (24 December 2019 and 13 January 2020) and geographic location (primarily Wuhan city, Hubei Province, China) suggested a potentially large 'first generation' human-to-human virus transmission. Li, Zai et al. (J Med Virol 2020, see ***below***) estimated that SARS-CoV-2 likely originated in Wuhan on 9 November 2019 (95% credible interval: 25 September 2019 and 19 December 2019). Li, Wang et al. (J Med Vir 2020, see ***below***) confirmed the recent and rapid human-to-human transmission, with estimates of virus emergence ranging from 15 October to 10 November 2019 or 16 November to 22 December 2019 depending on the calculation method.

Paraskevis (Infect Genet Evol 2020, see ***below***) described the lack of a mosaic relationship of SARS-CoV-2 to the closely related sarbecoviruses, indicating the lack of a recombination event in the emergence of SARS-CoV-2. Hence, SARS-CoV-2 likely emerged from the accumulation of mutations responding to altered selective pressures or from the infidelity of RNA polymerase perpetuated as replication-neutral mutations (Fahmi Infect Genet Evol. 2020, see ***below***).

Patino-Galindo (manuscript on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.02.10.942748v2) suggested a two-hit scenario in the emergence of the SARS-CoV-2 virus whereby the virus ancestors in bats first acquired genetic characteristics of SARS by incorporation of a SARS-like RBD through recombination before 2009, and subsequently, the lineage that led to SARSCoV-2 accumulated further, unique changes specifically in the RBD.

Gu (Virus Evol 2020, see ***below***) reported that the amino acid usage pattern of SARS-CoV-2 was generally found similar to bat and human SARSr-CoVs. He also found greater synonymous codon usage distance between SARS-CoV-2 and its phylogenetic relatives on S and M genes, suggesting these two genes of SARS-CoV-2 are subjected to different evolutionary pressures.

Based on an analysis of the 4 structural genes, Kandeel (J MedVir 2020, see ***below***) further reported that SARS-CoV-2 prefers pyrimidine rich codons to purines. Most high-frequency codons were found to end with A or T, while the low frequency and rare codons were ending with G or C. SARS-CoV-2 structural proteins showed 5-20 lower ENc values, compared with SARS, bat SARS and MERS-CoVs. This implies higher codon bias and higher gene expression efficiency of SARS-CoV-2 structural proteins. SARS-CoV-2 encoded the highest number of over biased and negatively biased codons. Pangolin β-CoV showed little differences with SARS-CoV-2 ENc values, compared with SARS, bat SARS and MERS CoV.

A manuscript by Zhang (on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.25.20027953v2) provided a hypothesis to explain the initial spread of the disease. Based on the analysis of 169 virus sequences, the authors were able to propose a classification of current SARS-CoV-2 isolates into two main types, with three sources of transmission, namely Type IA, Type IB, and Type II. Among them, Type IA corresponded to the earliest transmission source, which did not occur in the Huanan Market, indicating that the original transmission source was not from the Huanan Market. Type II came from the Huanan Market. As most samples detected belong to Type II, it was speculated that a Type II virus was the major outbreak source. By analysing the three genomic sites distinguishing Type I and Type II strains, it was found that the synonymous changes at two of the three sites conferred higher protein translational efficiencies to Type II strains. The authors speculated that this observation may be related to higher transmissibility of Type II strains.

Tang (preprint on National Science Review: https://academic.oup.com/nsr/advance-article/doi/10.1093/nsr/nwaa036/5775463?searchresult=1) presented additional data on the origin and evolution of SARS-CoV-2. Although the authors found only 4% variability in genomic nucleotides between SARS-CoV-2 and the bat SARSr-CoV RaTG13, the difference at neutral sites was 17%, suggesting the divergence between the two viruses was much larger than previously estimated. The report also suggested that new variations in functional sites in the receptor-binding domain (RBD) of the spike seen in SARS-CoV-2 and viruses from pangolin SARSr-CoVs are likely caused by mutations and natural selection besides recombination. Based on the analyses of 103 SARS-CoV-2 genomes, the authors confirmed the publication by Zhang (on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.25.20027953v2) indicating that these viruses evolved into two major types. These 2 types were here designated L and S, with the L type (~70%) being more prevalent than the S type (~30%), and the S type representing the ancestral version. Of note, both types of virus were detected outside China.

Yi (Clin Inf Dis 2020, see ***below***) used a different approach to the analysis of 84 sequences in GISAID to provide evidence for genetic recombination underlying the evolution of the virus.

While comparing ORF1ab polyprotein with other βCoVs, Cárdenas-Conejo (J Med Vir 2020, see ***below***) found a 42 amino acid signature that is only present in SARS-CoV-2. Members from clade 2 of sarbecoviruses have traces of this signature. The amino acid signature located in the acidic-domain of papain-like protein of SARS-CoV2 and bat-SL-RatG13 guided the authors to suggest that SARS-CoV-2 probably emerged by genetic drift from bat-SL-CoV-RaTG13. Lau, Luk et al. (Em Inf Dis 2020, see ***below***) noted that despite the close relatedness of SARS-CoV-2 to bat and pangolin viruses, none of the existing SARS-related CoVs represents its immediate ancestor. Most of the genome region of SARS-CoV-2 is closest to SARSr-Ra-BatCoV-RaTG13 from an intermediate horseshoe bat in Yunnan, whereas its RBD is closest to that of pangolin viruses. Potential recombination sites were identified around the RBD region, suggesting that SARS-CoV-2 might be a recombinant virus, with its genome backbone evolved from Yunnan bat virus-like SARS-related CoVs and its RBD region acquired from pangolin virus-like SARS-related CoVs.

Divergence dates between SARS-CoV-2 and the bat sarbecovirus reservoir were subsequently estimated as 1948 (95% highest posterior density (HPD): 1879–1999), 1969 (95% HPD: 1930–2000) and 1982 (95% HPD: 1948–2009), indicating

that the lineage giving rise to SARS-CoV-2 had been circulating unnoticed in bats for decades (Boni Nat MIcrob 2020, see ***below***).

Among the hypotheses to explain the origin of SARS-CoV-2, Xia (Mol Biol Evol 2020, see ***below***) observed that SARS-CoV-2 has the most extreme CpG deficiency in all known βCovs genomes. This suggests that SARS-CoV-2 may have evolved in a new host (or new host tissue) with high zinc finger antiviral protein expression. This observation allowed for an alternative hypothesis for the origin of SARS-CoV-2. The ancestor of SARS-CoV-2 and BatCoV RaTG13 might have infected the intestine of a mammalian species (e.g., canids). Then the presumably strong selection against CpG in the viral RNA genome in canid intestine may have resulted in rapid evolution of the virus, with many CpG→UpG mutations leading to reduced genomic ICpG and GC%. The licking of anal regions in canids during mating and other circumstances may facilitate viral transmission from the digestive system to the respiratory system. Finally, the reduced viral genomic ICpG may have allowed the virus to evade human zinc finger antiviral protein-mediated immune response and become a severe human pathogen.

In spite of these considerable research advancements, the origin of the virus remains ambiguous. Zhang (J Inf 2020, see ***below***) indicated that the source of the virus might be tracked in the following ways:

- Tracing back the viral emergence at the Huanan seafood market. It has been that the market has been closed for more than two months, but the government can list all merchants in the market and clarify which animals they sold, and what were the purchase channels of the animals. Thus, sampling the animals from their purchase channels appears feasible.
- Detection of the SARS-CoV-2-like virus in wild animals.
- Detection of serum antibody in clinical samples collected before December 2019 in Hubei Province, especially in Wuhan.

Additional important research is also focused on the identification of putative intermediate animal hosts, as presented in ***Host range & search for intermediate animal hosts*** below). Moreover, a report by J Cohen in July 2020 (Science Mag 2020, see: https://www.sciencemag.org/news/2020/07/who-led-mission-may-investigate-pandemic-s-origin-here-are-key-questions-ask) indicated that a WHO-led international mission was under preparation, in order to investigate the pandemic's origin.

Multiple reasons to rule out a laboratory origin

While speculations, rumours and conspiracy theories that SARS-CoV-2 is of laboratory origin circulate in social media, several publications point to the lack of credible evidence to support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV.

Liu (Emerg Micr Inf 2020, see ***below***), for instance, pointed to the fact that evolution is stepwise and accrues mutations gradually over time, whereas synthetic constructs would typically use a known backbone and introduce logical or targeted changes instead of the randomly occurring mutations that are present in naturally isolated viruses such as bat CoV RaTG13. However, the sequence data irrefutably show that SARS-CoV-2 is not derived from any previously used virus backbone. Hao (Emerg Microbes Inf 2020, see ***below***) ruled out a published claim that SARS-CoV-2 would have a unique inserted sequence (1378 bp) located in the middle of its S glycoprotein gene that had no match in other coronaviruses and that this unique sequence would be similar to some sequence in a common expression vector used in research laboratory.

Andersen (Nature Med 2020, see ***below***) added that while SARS-CoV-2 may bind human ACE2 with high affinity, computational analyses predict that the interaction is not ideal and that the RBD sequence is different from those shown in SARS-CoV to be optimal for receptor binding. Thus, the high-affinity binding of the SARS-CoV-2 S protein to

human ACE2 is most likely the result of natural selection on a human or human-like ACE2 that permits another optimal binding solution to arise. This is strong evidence that SARS-CoV-2 is not the product of purposeful manipulation.

In theory, it is also possible that SARS-CoV-2 acquired RBD mutations during adaptation to passage in cell culture, as has been observed in studies of SARS-CoV (Andersen Nature Med 2020, see ***below***). The finding of SARS-CoV-like coronaviruses from pangolins with nearly identical RBDs, however, provides a much stronger explanation of how SARS-CoV-2 acquired these via recombination or mutation. The acquisition of both the polybasic cleavage site and predicted O-linked glycans also argues against culture-based scenarios. New polybasic cleavage sites have been observed only after prolonged passage of low-pathogenicity avian influenza virus *in vitro* or *in vivo*. Furthermore, a hypothetical generation of SARS-CoV-2 by cell culture or animal passage would have required prior isolation of a progenitor virus with very high genetic similarity, which has not been described. Subsequent generation of a polybasic cleavage site would have then required repeated passage in cell culture or animals with ACE2 receptors similar to those of humans, but such work has also not previously been described. Finally, the generation of the predicted O-linked glycans is also unlikely to have occurred due to cell-culture passage, as such features suggest the involvement of an immune system.

Sequence diversity among isolates

Initial observations in China

Among the first data generated at the beginning of the outbreak, virus isolates from five patients with severe pneumonia (hospitalized from December 18 to December 29, 2019 at Jin Yin-tan hospital in Wuhan) revealed 99.8-99.9% nucleotide identities (Ren Chinese Med J 2020, see ***below***). Zhou (Nature 2020, see ***below***) also reported more than 99.9% identity among isolates obtained from 7 patients, Lu (Lancet 2020, see ***below***) more than 99.98% sequence identity among 10 genome sequences obtained from nine patients, and Ceraolo (J MedVir 2020, see ***below***) >99% sequence similarity among 56 genomes. Of note, at least two hyper-variable genomic hotspots were detected, one of which responsible for a Serine/Leucine variation in the viral ORF8-encoded protein. Another study conducted on 32 genomes of strains sampled from China, Thailand, and USA between 24 December 2019 and 23 January 2020 suggested increasing tree-like signals from 0 to 8.2%, 18.2%, and 25.4%) overtime also provided early evidence of increasing genetic diversity of SARS-CoV-2 in human hosts (Li, Wang et al. J Med Vir 2020, see ***below***).

Following the analysis of 54 gene sequences, Wen (J Infect 2020, see ***below***) noted the hyper-variable genomic hotspot to be established in the SARS-CoV-2 population at the nucleotide but not the amino acid level, suggesting that there beneficial mutations had not been acquired. Of note, nsp1, nsp3, and nsp15 of ORF1ab and gene S were found to carry significantly more mutations than other genes. Subsequently, Wang (J Med Vir 2020, see ***below***) reported on the analysis of 95 full-length genomic sequences of SARS-CoV-2 strains from NCBI and GISAID databases. The homology among all viral strains was generally high, among them 99.99% (99.91%-100%) at the nucleotide level, 99.99% (99.79%-100%) at the amino acid level. Although overall variation in ORF regions was low, 13 variation sites in 1a, 1b, S, 3a, M, 8, and N regions were identified, among which positions nt28144 in ORF 8 and nt8782 in ORF 1a showed mutation rate of 30.53% (29/95) and 29.47% (28/95) respectively.

Sequence-based surveillance and resources

Monitoring the virus sequence diversity among the newest isolates remains an important component of COVID-19 surveillance. The number of sequences deposited to GISAID increased rapidly after the first virus identification. By October 20 2020 12:00 CET, a total of 151 535 sequences has been reached (see https://www.gisaid.org/).

In addition to GISAID, other resources became available for SARS-CoV-2 sequence analysis. The Nextstrain team analyzes virus sequence data on a global and continental level, and the Nextclade tool has been designed to compare new sequences to the SARS-CoV-2 reference sequence, assign them to clades, and see where they fall on a the SARS-CoV-2 tree (https://nextstrain.org/sars-cov-2/).

The website of the China National Center for Bioinformation (https://bigd.big.ac.cn/ncov?lang=en), available in Chinese and English, constitutes another useful resource on SARS-CoV-2 sequences. Another resource described by Cleemput (Bioinform 2020, see ***below***) is the Genome Detective Coronavirus Typing Tool, available at https://www.genomedetective.com/app/typingtool/cov, which can accurately identify SARS-CoV-2 sequences isolated in China and around the world.

Intra-host variants of SARS-Cov-2

Following metatranscriptome sequencing for the bronchoalveolar lavage fluid of SARS-CoV-2 patients, Shen (Clin Inf Dis 2020, see ***below***) presented data suggesting that SARS-CoV-2 evolves *in vivo* after infection. The median number of intra-host variants was 1-4 in SARS-CoV-2 infected patients, ranging between 0 and 51 in different samples. The distribution of variants on genes was similar to those observed in the population data (110 sequences). However, very few intra-host variants were observed in the population as polymorphism, implying either a bottleneck or purifying selection involved in the transmission of the virus, or a consequence of the limited diversity represented in the current polymorphism data.

Bal (Clin Microb Inf 2020, see ***below***), characterized whole genome sequences of SARS-CoV2 isolated from an asymptomatic patient, in 2 clinical samples collected 1 day apart. Comparison of these sequences suggested viral evolution with development of quasispecies. The study also identified a new deletion in nsp2 (Asp268Del). The analysis of 571 whole genome sequences identified this deletion in 37 other viruses collected in England (February) and in Netherlands (March), suggesting the spread of this deletion in Europe.

Viral mutations

According to Rambaut (Nature Microb 2020, see ***below***; https://cov-lineages.org/), the earliest lineage A viruses, such as Wuhan/WH04/2020 (EPI_ISL_406801), sampled on 5 January 2020, share two nucleotides (positions 8,782 in ORF1ab and 28,144 in ORF8) with the closest known bat viruses (RaTG13 and RmYN02). Different nucleotides are present at those sites in viruses assigned to lineage B, of which Wuhan-Hu-1 (GenBank accession no. MN908947) sampled on 26 December 2019 is an early representative. Hence, although viruses from lineage B happen to have been sequenced and published first, it is likely (based on current data) that the most recent common ancestor (MRCA) of the SARS-CoV-2 phylogeny shares the same genome sequence as the early lineage A sequences (for example, Wuhan/WH04/2020).

Multiple mutations have been described in subsequent virus isolates. For instance, Benvenuto (J inf 2020, see ***below***) found in more recent isolates the presence of two mutations affecting NSP6 and ORF 10 adjacent regions. Amino acidic change stability analysis suggests both mutations could confer lower stability of the protein structures.

In another example, Sheikh (Infect Genet Evol. 2020, see ***below***) observed the 5' terminal of the genome to be more variable and prone to mutations, as compared to the 3' terminal. ORF1ab, S, ORF3a and E appeared as key drivers of diversity among strains with RBD of S emerging as mutational hotspot.

Using the epitope information along with variants of the virus, Koyama (Pathog 2020, see ***below***) found several variants which might cause drifts. Among such variants, 23403A>G variant (p.D614G) in S protein B-cell epitope appeared to be observed frequently in European countries, such as the Netherlands, Switzerland, and France, but seldom observed in China. A subsequent analysis of over 1 225 SARS-CoV-2 genomes spanning from late December 2019 to mid-March 2020 (Isabel Sci Rep 2020, see ***below***). The D614G mutation was reported as a predominant clade in Europe (954 of 1449, i.e. 66%, sequences) and spreading worldwide (1237 of 2795, 44%, sequences). Molecular dating analysis estimated the emergence of this clade around mid-to-late January (10-25 January) 2020.

Eaaswarkhanth (Int J Infect Dis 2020, see ***below***) speculated that the S-G614 strains may be more virulent, increasing the severity in infected individuals, especially in Europe where this mutation is prominent. In line with this hypothesis,

Zhang (manuscript on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.06.12.148726v1) observed that retroviruses pseudotyped with S-G614 infected ACE2-expressing cells markedly more efficiently than those with S-D614. This greater infectivity was correlated with less S1 shedding and greater incorporation of the S protein into the pseudovirion. Similar results were obtained using the virus-like particles produced with SARS-CoV-2 M, N, E, and S proteins. However, S-G614 did not bind ACE2 more efficiently than S-D614, and the pseudoviruses containing these S proteins were neutralized with comparable efficiencies by convalescent plasma. S-G614 was shown more stable than S-D614, consistent with epidemiological data suggesting that viruses with S-G614 transmit more efficiently. Similarly, Daniloski (manuscript on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.06.14.151357v2) produced SARS-CoV-2-pseudotyped lentiviral particles (S-Virus) with variant and with S-D614. The authors showed that in multiple cell lines, including human lung epithelial cells, that pseudovirus carrying the S-G614 mutation was up to 8-fold more effective at transducing cells than wild-type pseudovirus. However, according to Isabel, *in silico* analyses on the S protein structure suggested that the mutation is most likely neutral to protein function as it relates to its interaction with the human ACE2 receptor (Sci Rep2020, see ***below***).

Benedetti (J Transl Med 2020, see ***below***) identified SARS-CoV-2 genome sequences carrying a previously unknown deletion of 9 nucleotides in position 686-694 of nsp1, corresponding to AA position 241-243 (KSF). This deletion was found in different geographical areas. Structural prediction modelling suggests an effect on the C-terminal region of the protein, important for regulation of viral replication and negative effect on host's gene expression. In addition, substitution of the two amino acids (KS) from nsp1 of SARS-CoV was previously reported to revert loss of IFN-α expression. This observation confirms that SARS-CoV-2 is undergoing profound genomic changes.

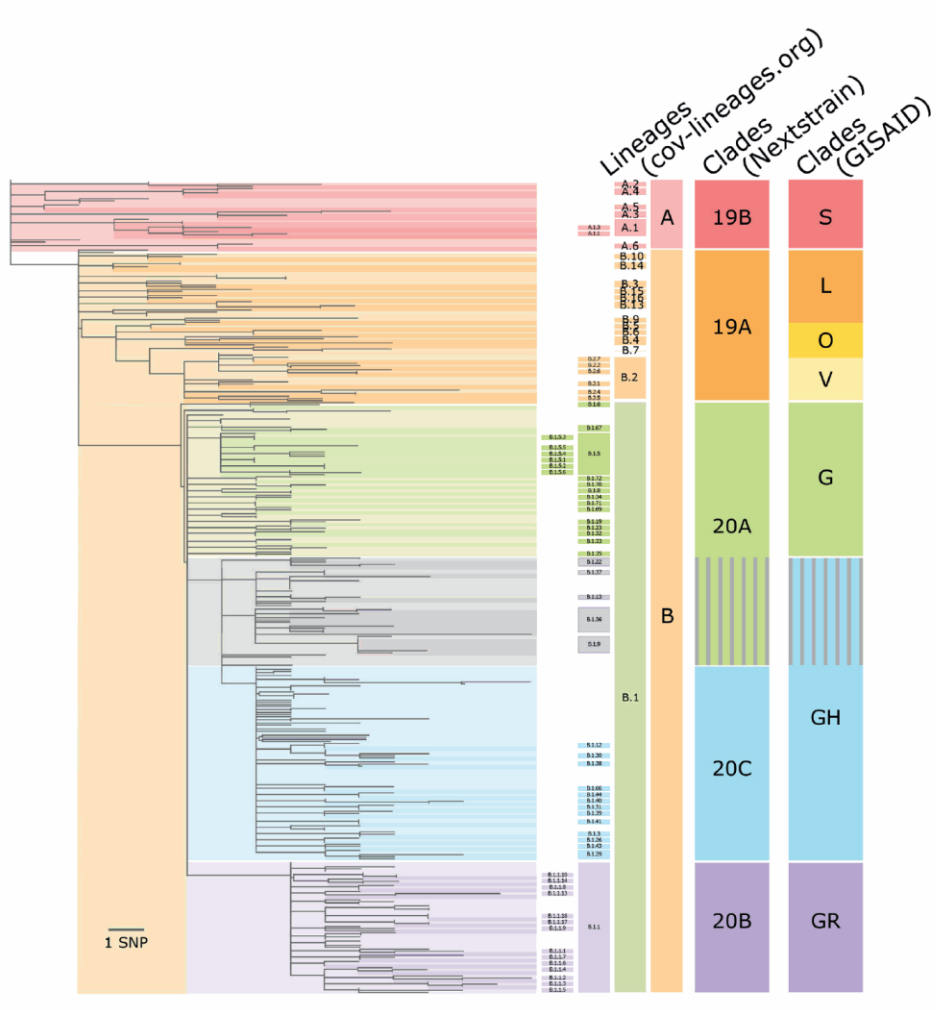
Of note, a study by MacLean (manuscript on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.05.28.122366v2) suggested that the vast majority of observed mutations occur at low frequency, with only ~10% of mutations observed in more than six of 15537 sequences.

Clade nomenclatures for SARS-CoV-2

Phylogenetic analyses soon identified the circulation of different clades of SARS-CoV-2. In a publication available online from April 24 2020, Sheikh (Infect Genet Evol. 2020, see ***below***) already revealed at least five different clades circulating. Rambaut (Nature Microb 2020, see ***below***; https://cov-lineages.org/) suggested a nomenclature system with the two major lineages of SARS-CoV-2 denoted as lineages A and B (see ***Viral*** mutations above).

However, as reviewed by Alm (EuroSurv 2020, see ***below***), alternative nomenclature systems have been proposed, including those by Nextstrain (https://nextstrain.org/sars-cov-2/) and GISAID (https://www.gisaid.org/references/statements-clarifications/clade-and-lineage-nomenclature-aids-in-genomic-epidemiology-of-active-hcov-19-viruses/). Nextstrain and GISAID clade nomenclatures aim at providing a broad-brush categorisation of globally circulating diversity, while the lineages of Rambaut are meant to correspond to outbreaks. The relation between the three nomenclatures is illustrated in ***Figure 4.***

Figure 4. Schematic comparison of the GISAID, Nextstrain and cov-lineages.org nomenclatures for SARS-CoV-2 sequences, February–July 2020 (from Alm EuroSurv 2020)



Sequence homology of the S gene

The S gene of SARS-CoV-2 appears highly divergent to other CoVs, with less than 75% nucleotide sequence identity to all previously described SARS-CoVs, except a 93.1% nucleotide identity to RaTG13 (Zhou Nature 2020, see ***below***). The S genes of SARS-CoV-2 and RaTG13 S gene are longer than other SARS-CoVs. The major differences in SARS-CoV-2 are three short insertions in the N-terminal domain, and 4/5 key residues changes in the receptor-binding motif, in comparison with SARS-CoV.

At the level of amino acids, the S glycoprotein of SARS-CoV-2 was found to have 76.3% identity and 87.3% similarity with the S glycoprotein of SARS-CoV (Baruah J Med Virol 2020, see ***below***).

The S2 subunit of SARS-CoV-2 was found highly conserved, sharing 99% sequence identity with those of the two bat SARS-like CoVs (SL-CoV ZXC21 and ZC45) and human SARS-CoV (Chan Em Micr Inf 2020, see ***below***). This observation suggests that broad spectrum antiviral peptides against S2 may be considered as therapeutic candidates.

The S1 subunit of SARS-CoV-2 shares around 70% identity to that of the two bat SARS-like CoVs and human SARS-CoV. The core domain of the receptor binding domain (RBD) (excluding the external subdomain) is highly conserved, but the external subdomain of the SARS-CoV-2 RBD (which is responsible for the direct interaction with the host receptor) shares only 40% amino acid identity with other SARS-related coronaviruses. Of note, homology modelling in another study revealed that SARS-CoV-2 has a similar RBD structure to that of SARS-CoV, despite amino acid variation at some key residues (Lu Lancet 2020, see ***below)***. Moreover, several critical residues in SARS-CoV-2 RBD (particularly Gln493)

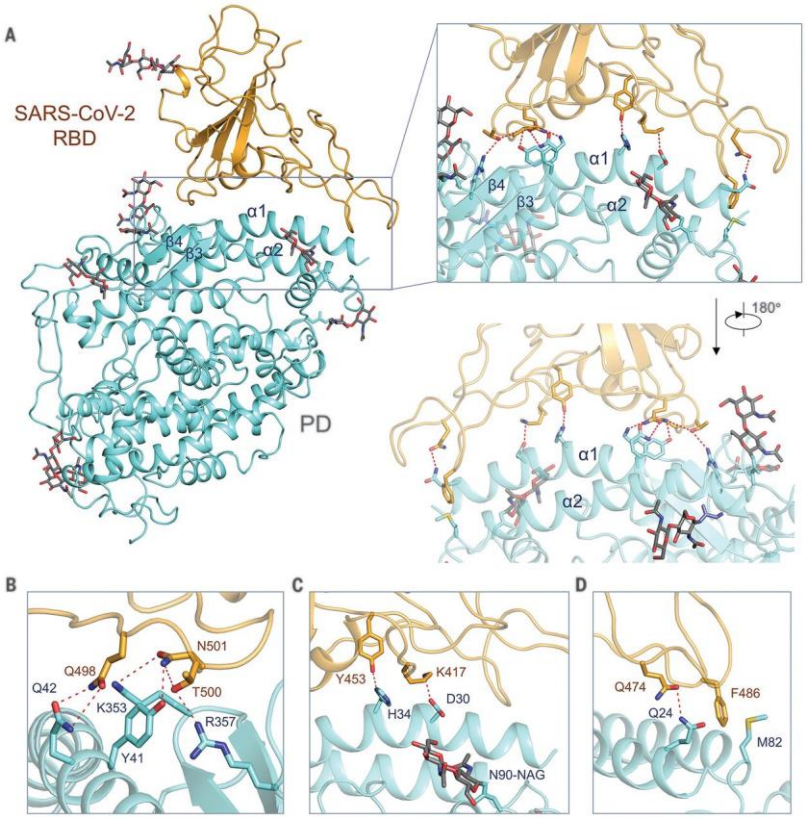
provide favourable interactions with human ACE2, consistent with SARS-CoV-2's capacity for human cell infection (Wan J Virol 2020, see ***below***). Several other critical residues in SARS-CoV-2 RBD (particularly Asn501) are compatible with, but not ideal for, binding human ACE2.

Structure of S and interactions with the ACE2 receptor

Wrapp (Science 2020, see ***below***) disclosed the 3.5 Å-resolution cryo-EM structure of the SARS-CoV-2 S trimer in the prefusion conformation. The predominant state of the trimer has one of the three receptor-binding domains (RBDs) rotated up in a receptor-accessible conformation. He also showed biophysical and structural evidence that SARS-CoV-2 S binds ACE2 with higher affinity than SARS-CoV S. Additionally he tested several published SARS-CoV RBD-specific monoclonal antibodies and found that no appreciable binding to SARS-CoV-2 S, confirming previous conclusions from sequence analyses that antibody cross-reactivity may be limited between the two virus RBDs.

Yan (Science 2020, see ***below***) presented the cryo-EM structures of full-length human ACE2, in the presence of a neutral amino acid transporter B0AT1, with or without the receptor binding domain (RBD) of the surface S glycoprotein (S protein) of SARS-CoV-2, both at an overall resolution of 2.9 Å, with a local resolution of 3.5 Å at the ACE2-RBD interface. The ACE2-B0AT1 complex is assembled as a dimer of heterodimers, with the Collectrin-like domain (CLD) of ACE2 mediating homo-dimerization (see ***Figure 5***). The RBD is recognized by the extracellular peptidase domain (PD) of ACE2 mainly through polar residues.

Figure 5 Interactions between SARS-CoV-2-RBD and ACE2 (from Yan Science 2020).



(A) The PD of ACE2 mainly engages the α1 helix in the recognition of the RBD. The α2 helix and the linker between β3 and β4 also contribute to the interaction. Only one RBD-ACE2 is shown. (B to D) Detailed analysis of the interface between SARS-CoV-2-RBD and ACE2. Polar interactions are indicated by red dashed lines. NAG, N-acetylglucosamine.

The structural basis of ACE2 receptor recognition by SARS-CoV-2 was further investigated by Shang (Nature 2020, see ***below***) and Lan (Nature 2020, see ***below***). Compared with the SARS-CoV RBD, a human ACE2-binding ridge in SARS-CoV-2 RBD was found to take a more compact conformation; moreover, several residue changes in SARS-CoV-2 RBD

stabilize two virus-binding hotspots at the RBD/hACE2 interface. These structural features of SARS-CoV-2 RBD enhance its hACE2-binding affinity. The same observation was made by Wang (Cell 2020, see ***below***).

Letko (Nature Microb 2020, see ***below***) confirmed previous observations in terms of receptor usage of the virus, and suggested that SARS-CoV-2 is capable of using human ACE2 efficiently, which may help to explain human-to-human transmissibility. The experiments were based on the use of pseudotypes and investigated the mechanism of entry of a whole set of lineage B βCoVs.

Ibrahim (J Inf 2020, see ***below***) developed predictions of the COVID-19 S binding site to the cell-surface receptor (Glucose Regulated Protein 78 (GRP78)). The study revealed that binding is more favourable between regions III (C391-C525) and IV (C480-C488) of the spike protein model and GRP78. Region IV was found the main driving force for GRP78 binding with the predicted binding affinity of -9.8 kcal/mol. These nine residues could be used to develop therapeutics specific against COVID-19.

Of note, Xia (Cell Mol Immunol 2020, see ***below***) published a report on the fusion mechanism of SARS-CoV-2 and fusion inhibitors targeting HR1 domain in S protein.

Watanabe (Science 2020, see ***below***) revealed the **glycan structures** on a recombinant SARS-CoV-2 S immunogen. This analysis enabled mapping of the glycan-processing states across the trimeric viral S. Shielding of the receptor binding sites on the SARS-CoV-2 spike by proximal glycosylation sites (N165, N234, N343) could be observed. The shielding of receptor binding sites by glycans is a common feature of viral glycoproteins (observed for instance on SARS-CoV-1 S). While the oligomannose-type glycan content (28%) was found above that observed on typical host glycoproteins, it was lower than that of other viral glycoproteins. Overall, this glycosylation analysis of SARS-CoV-2 offers a detailed benchmark of site-specific glycan signatures characteristic of a natively folded trimeric S.

Other SARS-CoV-2 genes and proteins

A manuscript by Alam (Front Cell Infect Microbiol 2020, see ***below***) showed the conservation of the **E gene**, differing between SARS and SARS-Cov2 with a difference of single amino acid substitution and a single amino acid insertion present in SARS but absent from SARS-CoV-2. The authors recommended diagnosis to be based on this protein.

The **RNA-dependent RNA polymerase** (RdRp, also named **nsp12**) is the central component of coronaviral replication/transcription machinery. Gao (Science 2020, see ***below***) reported the cryo-EM structure of the full-length viral nsp12 in complex with cofactors nsp7 and nsp8 at 2.9-Å resolution. In addition to the conserved architecture of the polymerase core of the viral polymerase family, nsp12 possesses a newly identified β-hairpin domain at its N terminus. The structure provides a basis for the design of new antiviral therapeutics targeting viral RdRp.

Immunity to SARS-CoV-2 infection

While information pertaining to immune responses to SARS-CoV-2 remained scarce in the first months of the epidemic, an increasing amount of data is now available to characterize both innate and adaptive immune responses to the virus (see for instance Vabret Immunity 2020 ***below***). Such knowledge can be expected to facilitate vaccine development as well as specific immunotherapy against COVID-19.

Epitope predictions

Immune-informatics approaches targeting identification of T and B cell epitopes of SARS-CoV-2 have been described by numerous authors. For instance:

- Baruah (J Med Virol 2020, see ***below***) predicted five CTL epitopes, three sequential B cell epitopes and five discontinuous B cell epitopes in the S glycoprotein. Simulations suggested that the CTL epitopes bind MHC class I peptide-binding grooves via multiple contacts, with continuous hydrogen bonds and salt bridge anchors,

supporting their potential in generating immune responses. Of note, the study found only one overlapping CTL epitope between MERS-CoV and SARS-CoV-2 with one gap and one mismatch (Y-LQPRTFLL/YKLQPLTFLL), and no comparable epitopes with SARS-CoV.

- Kumar (manuscript on Preprints: https://www.preprints.org/manuscript/202002.0071/v1) predicted 8 B cell epitopes in the S protein based on the antigenicity score by using Vaxigen 2.0, some of which displayed overlap with those predicted by Baruah.
- Bojin (on Preprints : https://www.preprints.org/manuscript/202002.0102/v1) identified multiepitope peptides that can potentially trigger both CD4+ and CD8+ T cell immune responses.
- The approach selected by Ahmed (Vir 2020, see ***below***) focused on one side on S and N epitopes conserved across isolates and T cell epitopes offering broad coverage.
- Fast (on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.02.19.955484v2) reported the use of various computational tools from structural biology and machine learning to identify SARS-CoV-2 epitopes based on viral protein antigen presentation and antibody binding properties. The study identified two potential neutralizing B-cell epitopes near the spike protein RBD (positions 440-460 and 494-506) and a whole set of potential MHC I and II epitopes.
- Additional epitope predictions were also reported by Bhattacharya (J Med Virol 2020, see ***below***).
- Grifoni (Cell Host & Micr 2020, see ***below***) identified multiple specific regions in SARS-CoV-2 that have high homology to SARS-CoV. Parallel bioinformatic predictions identified a priori potential B and T cell epitopes for SARS-CoV-2. The authors suggested that independent identification of the same regions using two approaches reflects the high probability that these regions are promising targets for immune recognition of SARS-CoV-2. In this study, 10 B cell epitopes were identified with high sequence similarity between SARS-CoV and SARS-CoV-2. Five of these epitopes were found in the S protein, two in the membrane protein, and three in the nucleocapsid (N) protein. T cell epitopes were mostly found in the S protein and N protein.
- Using the concept of nullomer and introducing a distance from human self, Santoni (J Imm Meth 2020, see ***below***) provided a list of peptides that could deserve experimental investigation.
- Tilocca (Microbes Infect 2020, see ***below***) analysed SARS-CoV-2 N protein epitopes in taxonomically related coronaviruses.
- Using a Q-UEL system to access relevant literature, Robson (Comput Biol Med 2020, see ***below***) found the KRSFIEDLLFNKV epitope to be particularly well conserved
- Adding to an already long list of SARS-CoV-2 predicted epitopes, Joshi (Inform Med Unlocked 2020, see ***below***) proposed an epitope, ITLCFTLKR, for use as a potential vaccine candidate against SARS-COV-2. This epitope was found to have a 99.8% structural favourability as per Ramachandran-plot analysis and suitable population coverage.
- Kiyotani (J Hum Genet. 2020, see ***below***) authors found that four epitopes, S1060-1068, S1220-1229, N222-230, and N315-324 of SARS-CoV-2, have exactly same sequences reported as immunogenic SARS-CoV-derived epitopes for HLA-A*02:01, that correspond to S1042-1050, S1203-1211, N223-231, and N317-325 of SARS-CoV, respectively. Two epitopes in ORF1ab, ORF1ab2168-2176, and ORF1ab4089-4098 (which is conserved in SARS-CoV) were predicted to have a strong affinity to HLA-A*24:02 as well as HLA-A*02:01 and HLA-A*02:06. Based on their allele frequency, these epitopes could cover 83.8% of the Japanese individuals. Since no mutation was identified in these epitope sequences, these were considered to possibly contribute to the development of rationally designed vaccines against SARS-CoV-2.
- More recently, Oladipo, in an effort to develop a multiepitope vaccine, also predicted T cells and B cells epitopes, based on *in silico* analyses (Oladipo Inform Med Unlocked 2020, see ***below***).

Observations in COVID-19 patients

Thevarajan (Nat Med 2020, see ***below***) reported the kinetics of the immune response in relation to clinical and virological features of a patient with mild-to-moderate COVID-19 requiring hospitalisation. Increased antibody-secreting cells, follicular T-helper cells, activated CD4+ and CD8+ T-cells and IgM/IgG SARS-CoV-2-binding antibodies (immunofluorescence assay using SARS-CoV-2-infected Vero cells) were detected in blood, prior to symptomatic recovery. These immunological changes persisted for at least 7 days following full resolution of symptoms. Of note, the authors detected reduced frequencies of CD16+ CD14+ monocytes in peripheral blood at day 7-9, which might indicate efflux of CD16+CD14+ monocytes from blood to the site of infection. Low levels of activated HLA-DR+ CD3-CD56+ NK cells were found in both the COVID-19 patient and healthy controls.

Comparisons between symptomatic and asymptomatic subjects

Carsetti (manuscript on medRxiv, see https://www.medrxiv.org/content/10.1101/2020.06.22.20137141v1) performed a longitudinal follow-up analysis of innate and adaptive immunity in 64 adults with a spectrum of clinical presentations (28 healthy SARS-CoV-2-negative contacts of COVID-19 cases; 20 asymptomatic SARS-CoV-2-infected cases; 8 patients with mild COVID-19 disease and 8 cases of severe COVID-19 disease). The data showed that high frequency of NK cells and early and transient increase of specific IgA and, to a lower extent, IgG were associated to asymptomatic SARS-CoV-2 infection. By contrast, monocyte expansion and high and persistent levels of IgA and IgG, produced relatively late in the course of the infection, characterized severe disease. Modest increase of monocytes and rapidly declining antibodies were detected in mild COVID-19.

Similarly, Long (Nature Med 2020, see ***below***) studied 37 asymptomatic individuals who were diagnosed with RT-PCR-confirmed SARS-CoV-2 infection. The asymptomatic group had a significantly longer duration of viral shedding than the symptomatic group. The virus-specific IgG levels in the asymptomatic group (median S/CO, 3.4; IQR, 1.6–10.7) were significantly lower (P = 0.005) relative to the symptomatic group (median S/CO, 20.5; IQR, 5.8–38.2) in the acute phase. Of asymptomatic individuals, 93.3% (28/30) and 81.1% (30/37) had reduction in IgG and neutralizing antibody levels, respectively, during the early convalescent phase, as compared to 96.8% (30/31) and 62.2% (23/37) of symptomatic patients. Forty percent of asymptomatic individuals became seronegative and 12.9% of the symptomatic group became negative for IgG in the early convalescent phase. In addition, asymptomatic individuals exhibited lower levels of 18 pro- and anti-inflammatory cytokines. These data suggest that asymptomatic individuals had a weaker immune response to SARS-CoV-2 infection.

Antibody response

In the first weeks of the epidemic, various studies characterized the kinetics, antigen specificity and isotype profile of the humoral response raised by SARS-CoV-2 infections.

By using an ELISA based assay using the recombinant viral nucleocapsid, Guo (Clin Inf Dis 2020, see ***below***) examined the host humoral response against SARS-CoV-2 including IgA, IgM and IgG responses. A total of 208 plasma samples were collected from 82 confirmed and 58 probable cases. The diagnostic value of IgM was evaluated in this cohort. The median times of IgM and IgA antibody detection were 5 days (IQR 3-6), while IgG was detected on 14 days (IQR 10-18) after symptom onset, with a positive rate of 85.4%, 92.7% and 77.9% respectively. In confirmed and probable cases, the positive rates of IgM antibodies were 75.6% and 93.1%, respectively. The detection efficiency by IgM ELISA was higher than that of qPCR method after 5.5 days of symptom onset. The positive detection rate was significantly increased (98.6%) when combined IgM ELISA assay with PCR for each patient compare with a single qPCR test (51.9%).

Yu (Eur Respir J 2020, see ***below***) analysed SARS-CoV-2 S protein-specific IgA, IgM and IgG antibodies by chemiluminescent immunoassay in 183 samples from 37 patients. The positive rate of antibodies was 98.9%, 93.4% and 95.1%, for IgA, IgM and IgG, respectively. The seroconversion rate for IgA, IgM or IgG was 100% 32 days after

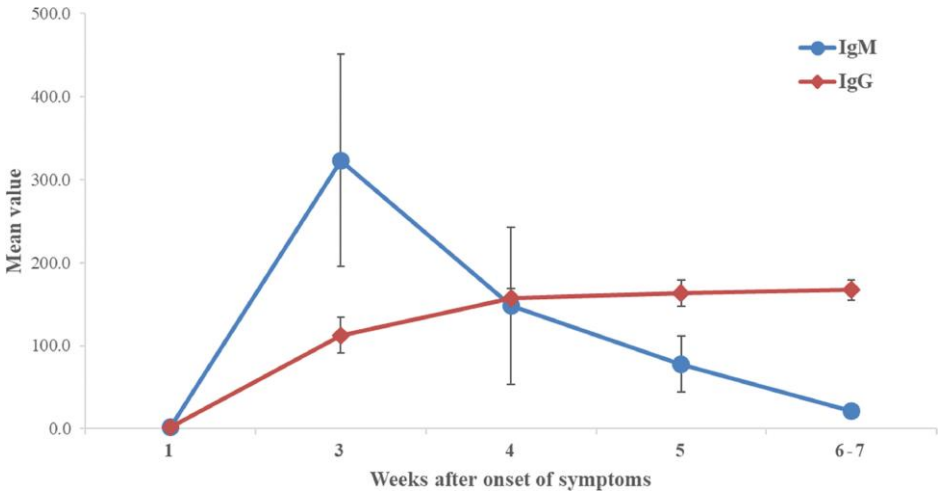
symptom onset, and the median conversion time for IgA, IgM and IgG was 13, 14 and 14 days, respectively. The relative levels of IgA and IgG were significantly higher in severe patients compared to non-severe patients.

Padoan (Clin Chim Acta 2020, see ***below***) evaluated the kinetics of IgM, IgA and IgG SARS-CoV-2 antibodies in COVID-19 patients with confirmed (rRT-PCR) infection. The authors found that the IgA response appears and grows early, peaks at week 3, and it is stronger and more persistent than the IgM response.

Immunology testing was also performed in 16 patients in Hong Kong using serum samples collected 14 days or longer after symptom onset (To Lancet Inf Dis 2020, see ***below***). The following rates of seropositivity were reported: 94% for anti-N IgG (n=15), 88% for anti-N IgM (n=14), 100% for anti-RBD IgG (n=16), and 94% for anti-RBD IgM (n=15). Anti-SARS-CoV-2-N or anti-SARS-CoV-2-RBD IgG levels correlated with virus neutralization titre (R^2>0·9). Of note, Pecora (Clin Lab Med 2020, see ***below***) observed that there are conflicting reports regarding the kinetics of anti-N and anti-S antibody detection. Some reports have shown detection of anti-N slightly earlier than anti-S antibodies, whereas others have shown the contrary, possibly because of differences in assay format

An early report by Xiao (J Inf 2020, see ***below***) presented the kinetics of IgM and IgG responses in 34 patients (***Figure 6***).

Figure 6 Timeline of IgM and IgG antibodies level to SARS-CoV-2 from onset of symptoms (from Xiao J Inf 2020)



Wu (non-peer-reviewed manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.03.30.20047365v1) characterized antibody responses in a larger cohort of 175 COVID-19 recovered patients with mild symptoms. The levels and the time course of SARS-CoV-2-specific neutralizing antibodies (NAbs) (pseudotyped-lentiviral-vector-based neutralization assay) and the S-binding antibodies (ELISA using RBD, S1, and S2 proteins) were monitored in parallel. SARS-CoV-2-specific NAbs were detected in patients from day 10-15 after the onset of the disease and remained thereafter. No cross-reactivity with SARS-CoV was observed. The NAb titers correlated with the S-binding antibodies targeting S1, RBD, and S2 regions. Elderly and middle-age patients had significantly higher plasma NAb titers (P<0.0001) and S-binding antibodies (P=0.0003) than young patients. The NAb titers were positively correlated with plasma CRP levels but negatively correlated with the lymphocyte counts of patients at the time of admission, indicating an association between humoral response and cellular immune response.

Another study, by Klein (J Clin Invest 2020, see ***below***) reported substantial heterogeneity in the antibody response among potential convalescent plasma donors. Interestingly, sex, age and hospitalization emerged as factors that can be used to identify individuals with a high likelihood of having strong antiviral antibody levels.

Catalan-Dibene (Nature Reviews Immunology 2020, see ***below***) described a preprint by Ju, who demonstrated the existence of virus-specific memory B cells recognizing the RBD of SARS-CoV-2 S protein in infected patients. They observed cross-reactivity of antibodies from these patients against S proteins, but not against the RBD, of SARS-CoV-1 and MERS-CoV. Through single-cell sorting and BCR sequencing, they generated 206 SARS-CoV-2 RBD-specific monoclonal antibodies. Antibodies were from diverse families of immunoglobulin genes, without any apparent enrichment for specific families. Two clones showed 98-99% blocking of viral entry, which correlated with high competing capacity against ACE2 receptor.

Neutralizing antibody responses

Van der Heide (Nat Rev Imm 2020, see ***below***) referred to a very interesting manuscript on medRxiv reporting robust induction of SARS-CoV-2-specific neutralizing antibodies in 94% of 175 patients with clinically mild COVID-19. Compared with young patients, middle-aged and older patients in this cohort had higher titres of neutralizing and binding antibodies. As older patients are generally considered at greater risk of severe disease, the robust humoral responses in this cohort was interpreted as possibly explaining their apparent protection. Of note, 10 of 175 patients recovered without developing detectable neutralizing antibody titres, suggesting that antiviral binding antibodies and cellular immune responses can both result in convalescence.

Importantly, as demonstrated by Tan (Front Med 2020, see ***below***) using samples collected at 6-7 months post-infection in a pseudovirus assay, antibodies show no difference in blocking the cell-entry of the 614D and 614G variants of SARS-CoV-2. These data suggest that immunity developed from a 614D variant of SARS-CoV-2 may offer protection from the currently predominant 614D variant.

Persistence of antibodies

As presented above, Long (Nature Med 2020, see ***below***) described a decline in antibody titers in the convalescent phase of the disease, suggesting that antibodies to SARS-CoV-2 may fade quickly. Other reports confirmed this observation.

Prévost (manuscript on bioRxiv, see ***below***) performed a cross-sectional study on 98 SARS-CoV-2-infected individuals to evaluate humoral responses against SARS-CoV-2 S. The vast majority of infected individuals elicited anti-S antibodies within 2 weeks after the onset of symptoms. The levels of receptor-binding domain (RBD)-specific IgG persisted overtime, while the levels of anti-RBD IgM decreased after symptoms resolution. While most of individuals developed neutralizing antibodies within the first two weeks of infection, the level of neutralizing activity was significantly decreased over time.

Using sequential serum samples collected up to 94 days post onset of symptoms (POS) from 65 RT-qPCR confirmed SARS-CoV-2-infected individuals, Seow (manuscript on medRxiv, see https://www.medrxiv.org/content/10.1101/2020.07.09.20148429v1) showed seroconversion in >95% of cases and nAb responses when sampled beyond 8 days POS. The authors observed that the magnitude of the nAb response is dependent upon disease severity, but this was not found to affect the kinetics of the nAb response. Declining nAb titres were observed during the follow-up period. Whilst some individuals with high peak response (>10 000) maintained titres >1000 at >60 days POS, some with lower peak had titres approaching baseline within the follow up period. A similar decline in nAb titres was also observed in a cohort of seropositive healthcare workers from 2 hospitals.

Iyer (manuscript on medRxiv, see https://www.medrxiv.org/content/10.1101/2020.07.18.20155374v1) measured the kinetics of early antibody responses to the RBD of the S protein of SARS-CoV-2 in a cohort of 259 symptomatic North American patients (up to 75 days after symptom onset) compared to antibody levels in 1548 individuals whose blood samples were obtained prior to the pandemic. Between 14-28 days from onset of symptoms, IgG, IgA, or IgM antibody responses to RBD were all accurate in identifying recently infected individuals, with 100% specificity and a sensitivity

of 97%, 91%, and 81% respectively. Although the estimated median time to becoming seropositive was similar across isotypes, IgA and IgM antibodies against RBD were short-lived with most individuals estimated to become seronegative again by 51 and 47 days after symptom onset, respectively. IgG antibodies against RBD lasted longer and persisted through 75 days post-symptoms. IgG antibodies to SARS-CoV-2 RBD were highly correlated with nAbs targeting the S protein.

Tan (Front Med, see ***below***) confirmed these data by showing that 14 samples available at 6–7 months post-infection all showed significant neutralizing activities in a pseudovirus assay.

Cellular responses

Flow cytometry analyses

A study of the dynamic changes of lymphocyte subsets and cytokines profiles of 40 COVID-19 patients has been reported by Liu (EBioMed 2020, see ***below***). Significant decreases in the counts of T cells, especially CD8 + T cells, were observed as well as increases in IL-6, IL-10, IL-2 and IFN-γ levels in the peripheral blood in the severe cases compared to those in the mild cases. T cell counts and cytokine levels in severe COVID-19 patients who survived the disease gradually recovered at later time points to levels that were comparable to those of the mild cases.

Wang (J Inf Dis 2020, see ***below***) measured peripheral blood lymphocyte subsets in 60 hospitalized COVID-19 patients before and after treatment. Total lymphocytes, CD4+ T cells, CD8+ T cells, B cells and NK cells decreased in COVID-19 patients, and severe cases had a lower level than mild cases. The subsets (especially CD8+ T cells and CD4+/CD8+ ratio) showed a significant association with the inflammatory status. After treatment, 37 patients (67%) reached clinical response, with an increase of CD8+ T cells and B cells. In multivariate analysis, a post-treatment decrease of CD8+ T cells and B cells and an increase of CD4+/CD8+ ratio were indicated as independent predictors for poor efficacy.

Liao (Nat Med 2020, see ***below***) characterized the lung immune microenvironment with the bronchoalveolar lavage fluid (BALF) from 3 severe and 3 mild COVID-19 patients. The data show that monocyte-derived FCN1+ macrophages, but not FABP4+ alveolar macrophages that represent a predominant macrophage subset in BALF from patients with mild diseases, overwhelm in the severely damaged lungs from patients with acute respiratory distress syndrome (ARDS). These cells are highly inflammatory and enormous chemokine producers implicated in cytokine storm. Furthermore, the formation of tissue resident, highly expanded clonal CD8+ T cells in the lung microenvironment of mild symptom patients suggests a robust adaptive immune response.

Zheng, Zhang et al. (Cell Mol Imm 2020, see ***below***) provided a detailed analysis of the immunological characteristics of peripheral blood leukocytes from 16 patients, incl. 10 mild cases and 6 severe cases. The levels of **IFN-γ and TNF-α in CD4+ T cells** were lower in the severe group than in the mild group, whereas the levels of **granzyme B and perforin in CD8+ T cells** were higher in the severe group than in the mild group. The activation molecules showed no differences in CD4+ T cells, whereas the levels of **HLA-DR and TIGIT in CD8+ T cells** were higher in the severe group than in the mild group. These data indicate that COVID-19, similar to some chronic infections, damages the function of CD4+ T cells and promotes excessive activation and possibly subsequent exhaustion of CD8+ T cells. Compared with the healthy control and mild group, the frequency of multi-functional CD4+ T cells (positive for at least two cytokines) decreased significantly in the severe group. In CD8+ T cells, the frequency of the non-exhausted (PD-1−CTLA-4−TIGIT−) subset in the severe group was found significantly lower than that in the other two groups, an observation confirming a report by Zheng, Gao et al. (Cell Mol Imm 2020, see ***below***).

Virus-specific responses

Pia (Nat Rev Imm 2020, see ***below***) referred to a manuscript by Braun on medRxiv (subsequently published in Nature, see ***below***), which reported the characterization of **CD4+ T cell responses to SARS-CoV-2** in 18 patients with COVID-19 and 68 seronegative healthy donors. Peripheral blood mononuclear cells from patients and HDs were stimulated

with peptide pools derived from the SARS-CoV-2 S protein. S protein-specific CD4+ T cells could be detected in 83% of COVID-19 patients, as well as in 34% of healthy donors, albeit at lower frequencies. CD4+ T cells from patients with COVID-19 had a phenotype of recent activation in contrast to those from healthy donors. The authors suggest that S protein-specific T cells in healthy donors may be cross-reactive clones developed following a previous exposure to human endemic coronaviruses.

Using HLA class I and II predicted peptide 'megapools', Grifoni (Cell 2020, see ***below***) identified circulating SARS-CoV-2–specific CD8+ and CD4+ T cells in ~70% and 100% of COVID-19 convalescent patients, respectively. CD4+ T cell responses to S were robust and correlated with the magnitude of the anti-SARS-CoV-2 IgG and IgA titers. The M, spike and N proteins each accounted for 11-27% of the total CD4+ response, with additional responses commonly targeting nsp3, nsp4, ORF3a and ORF8, among others. For CD8+ T cells, spike and M were recognized, with at least eight SARSCoV-2 ORFs targeted. Confirming the data reported by Pia, the authors detected SARS-CoV-2–reactive CD4+ T cells in ~40-60% of unexposed individuals, suggesting cross-reactive T cell recognition between circulating 'common cold' coronaviruses and SARS-CoV-2.

Transcriptional changes

Ong (Cell Host Microbe 2020, see ***below***) profiled the transcriptional changes in a panel of immune genes in 3 COVID-19 patients and 10 healthy volunteers. Attenuated cytokine expression associated with mild infection was suggested to possibly delay T cell immunity against SARS-CoV-2, which would prolong infection, leading to the possibility that afebrile and undifferentiated COVID-19 cases may drive virus spread in the community.

Blanco-Melo (Cell 2020, see ***below***) compared the transcriptional response of SARS-CoV-2 to that of seasonal influenza A virus and respiratory syncytial virus in lung epithelium and transformed lung alveolar cells. The authors observed a significant lack of type I and III interferon (IFN-I and IFN-III) expression as compared to other respiratory viruses. Previous reports also demonstrated that coronaviruses hold mechanisms to evade host innate immune responses, in particular type I IFN signalling.

The data can be analysed in light of another publication by Hackbart (PNAS 2020, see ***below***), who demonstrated that a coronavirus endoribonuclease (EndoU) delays the activation of the host sensor system, by a mechanism where EndoU cleaves the 5-polyuridines from negative-sense viral RNA, which would otherwise be recognized by the cytosolic RNA sensor MDA5. Taken together, these findings suggest that SARS-CoV-2 can evade or delay antiviral immunity, ultimately leading to a dysregulated immune response and increased immunopathogenesis.

Wen (Cell Discov 2020, see ***below***) depicted a high-resolution transcriptome landscape of blood immune cell subsets during the recovery stage of COVID-19. It revealed that, compared to that in the healthy controls (HCs), monocytes containing high inflammatory gene expression and IL1β+ subsets predominated, whereas CD4+ T cells decreased remarkably in patients in the early recovery stage of COVID-19. We found that T and B cell clones were highly expanded during the recovery stage in COVID-19 patients.

Persistence of SARS-CoV-2-specific memory lymphocytes

Rodda (manuscript on medRxiv, see https://www.medrxiv.org/content/10.1101/2020.08.11.20171843v2) performed a longitudinal assessment of individuals recovered from mildly symptomatic COVID-19 to determine if they develop and sustain immunological memory against the virus. The authors found that recovered individuals developed virus-specific memory B and T cells that not only persisted, but in some cases increased numerically over three months following symptom onset. Furthermore, the SARS-CoV-2-specific memory lymphocytes exhibited characteristics associated with potent antiviral immunity: memory T cells secreted IFN-γ and expanded upon antigen re-encounter, while memory B cells expressed receptors capable of neutralizing virus when expressed as antibodies. These findings

demonstrated that mild COVID-19 elicits memory lymphocytes that persist and display functional hallmarks associated with antiviral protective immunity.

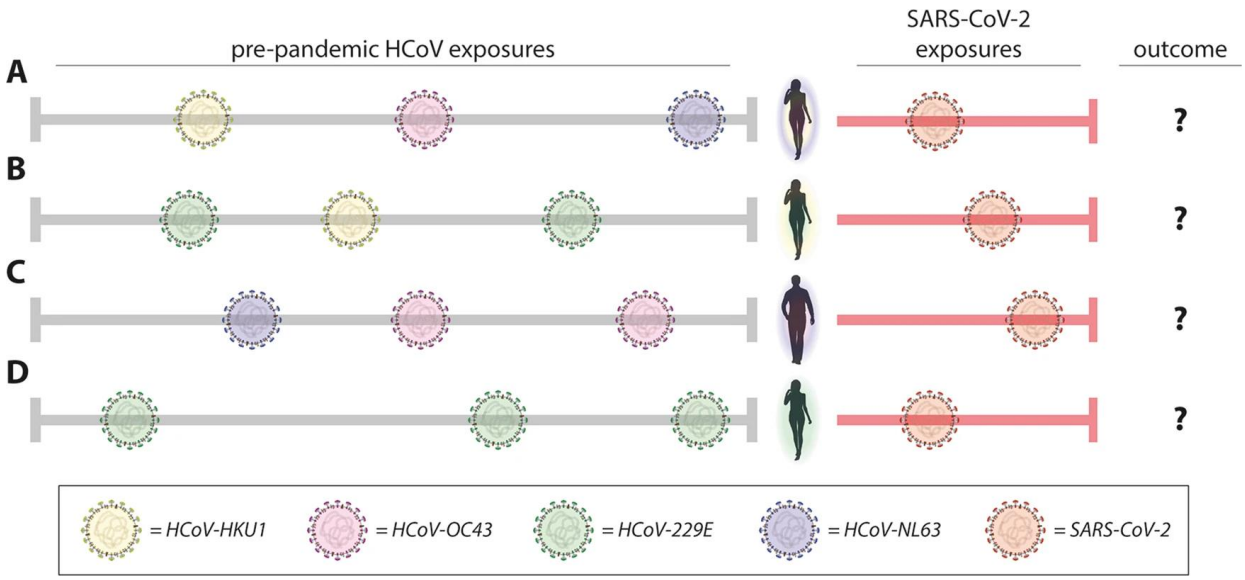
Tan (Front Med 2020, see ***below***) also suggested that a durable anti-SARS-CoV-2 cell-mediated immunity is common in the convalescent population. The authors found in 10 blood samples from cases at 6–7 months post-infection used for memory T-cell tests, that IFN- γ-producing CD4+ and CD8+ cells were increased upon SARS-CoV-2 antigen stimulation.

Immunity to other coronaviruses and cross-reactivity

Data pertaining to immunity against other coronaviruses could be very relevant to the understanding of immune responses to (and pathogenesis of) SARS-CoV-2. For instance, Wang (Virol Sin 2018, see ***below***) found antibodies against bat SARS-related coronavirus in people living near caves inhabited by bats in China. Serology testing against common human CoV strains was conducted in a prospective study of 200 subjects evaluated for respiratory infections in the U.S. (Gorse J Med Vir 2020, see ***below***). Interestingly, a publication by Chan (J Clin Virol 2009, see ***below***) presented the seroprevalence of HCoV HKU1 according to age, showing steadily increasing seroprevalence in childhood and early adulthood, from 0% in the < 10 years age group to a plateau of 21.6% in the 31-40 years age group in Hong Kong. More recently, Mateus (Science 2020, see ***below***) demonstrated that SARS-CoV-2 cross-reactive T-cell responses could be induced by infection with any of the circulating HCoVs: OC43, 229E, HKU1 or NL63.1

To what extent such pre-existing immunity may impact immune responses to SARS-CoV-2 remains to be better understood. De Vries (Signal Transd Targ Ther 2020, see ***below***) noted that pre-existing cross-reactive immunity may impact COVID-19 disease heterogeneity in different ways. At the moment it is unclear whether this is a positive or negative contribution, pre-existing cross-reactive immunity could either ameliorate or worsen COVID-19. As illustrated by ***Figure 7***, different pre-exposure history could lead to different cross-reactive responses and different disease severity.

Figure 7. Pre-existing cross-reactive T-cell immunity could impact COVID-19 disease severity (from de Vries Signal Transd Targ Ther 2020).



Of note, Kumakamba (manuscript on bioRxiv : https://doi.org/10.1101/2020.07.20.211664) reported the circulation of diverse α and βCoVs in Congo basin wildlife. Lacroix (Viruses 2020, see ***below***) in Guinea in frugivorous and insectivorous bats species and Maganga (Sci Rep 2020 , see ***below***) found α and βCoVs in cave-dewelling bats of Gabon ; all αCoVs sequences grouped with human CoV 229E (HCoV-229E). These findings suggest that CoVs are widely spread in Africa and their circulation should be assessed to evaluate the risk of exposure of potential zoonotic CoVs to humans. The exposure to and the consumption of wild animals infected with multiple strains of coronaviruses could also

potentially build a baseline level of immunity in communities relying on such a diet and explain to some extent the poor percolation of SARS-CoV-2 in human population in some countries.

Cross-reactivity of antibodies

In silico work and samples from immunized animals

Based on structure analyses, Tian (Em Inf Dis 2020, see ***below***) predicted potent binding of SARS-CoV-2 S protein by SARS-specific human monoclonal antibody CR3022. Yuan (Science 2020, see ***below***) determined the crystal structure of CR3022 in complex with the receptor-binding domain (RBD) of the SARS-CoV-2 S protein. CR3022 was found to target a highly conserved epitope, distal from the receptor-binding site, that enables cross-reactive binding between SARS-CoV-2 and SARS-CoV. However, *in vitro* experiments subsequently indicated the inability of CR3022 to neutralize SARS-CoV-2 (Manenti J Med Vir 2020, see ***below***).

Using MLV-based pseudotypes neutralization assays, Walls (Cell 2020, see ***below***) investigated the ability of plasma from four mice immunized with a stabilized SARS-CoV S to inhibit SARS-CoV-2 S- and SARS-CoV S-mediated entry into target cells. All sera tested completely inhibited transduction of SARS-CoV S-MLV and reduced SARS-CoV-2 S-MLV transduction to ~10% of control in Vero E6 cells. The elicitation of a heterotypic response blocking SARS-CoV-2 S-mediated entry into host cells concurred with the sequence and structural conservation of SARS-CoV-2 S and SARS-CoV S along with their comparable glycans shields and suggested that immunity against one virus of the sarbecovirus subgenus can potentially provide protection against related viruses.

Ou (Nature Comm 2020, see ***below***) also investigated antibody cross-reactivity between SARS-CoV-2 S and SARS-COV S. Polyclonal anti-SARS S1 antibodies T62 inhibited entry of SARS-CoV S- but not SARS-CoV-2 S-pseudovirions.

Human samples

Further studies by Ou (Nature Comm 2020, see ***below***) using recovered SARS and COVID-19 patients' sera showed limited cross-neutralization. Similarly, a serosurvey of a small number of healthy donors who provided samples prior to the emergence of SARS-CoV-2 indicated that pre-existing antibodies to common human CoVs show very little cross-reactivity to SARS-CoV-2 (St John J Immunol 2020, see ***below***). One preliminary study of a small cohort of SARS-CoV-2 immune individuals showed that there was no cross-reactivity of their Abs against the RBD of S protein from SARS-CoV or MERS-CoV, and no cross-neutralization of the viruses. Most cross-reactive Abs were directed at the S2 domain of S protein and the NP protein. However, a study on 98 SARS-CoV-2-infected individuals found that some of the elicited antibodies cross-reacted with other human coronaviruses in a genus-restrictive manner (Prévost, manuscript on bioRxiv, see ***below***).

Cross reactive T cells

Studies dissecting the human immune response against SARS-CoV-2 concluded that 20-50% of people who had not been exposed to SARS-CoV-2 had significant T cell reactivity directed against peptides corresponding to SARS-CoV-2 sequences (Le Bert Nature 2020, see ***below***; Grifoni Cell 2020, see ***below***; Meckiff on bioRxiv, see ***below***; Weiskopf Sci Immunol 2020, see ***below***; Braun Nature 2020, see ***below***). The studies were from geographically diverse cohorts (USA, Netherlands, Germany, Singapore, and UK), and the general pattern observed was that the T cell reactivity found in unexposed individuals was predominantly mediated by CD4+ T cells. Using human blood samples derived before the SARS-CoV-2 virus was discovered in 2019, Mateus (Science 2020, see ***below***) mapped 142 T cell epitopes across the SARS-CoV-2 genome and demonstrated a range of pre-existing memory CD4+ T cells that are cross-reactive with comparable affinity to SARS-CoV-2 and the common cold coronaviruses HCoV-OC43, HCoV-229E, HCoV-NL63, or HCoV-HKU1.

Innate immunity

Type I interferon

Lei (Nature 2020, see ***below***) showed that SARS-CoV-2 induces overt but delayed type-I interferon (IFN) responses. By screening 23 viral proteins, the authors found that SARS-CoV-2 NSP1, NSP3, NSP12, NSP13, NSP14, ORF3, ORF6 and M protein inhibit Sendai virus-induced IFN-β promoter activation, whereas NSP2 and S protein exert opposite effects. Further analyses suggested that ORF6 inhibits both type I IFN production and downstream signalling, and that the C-terminus region of ORF6 is critical for its antagonistic effect.

Zhang (Science 2020, see ***below***) provided strong evidence of the importance of type I IFN in the control of SARS-CoV-2, by showing that inborn errors of TLR3- and IRF7-dependent type I IFN immunity can underlie life-threatening COVID-19 pneumonia in patients with no prior severe infection. The authors indeed found an enrichment in rare variants predicted to be loss-of-function (LOF) at the 13 human loci known to govern TLR3- and IRF7-dependent type I interferon (IFN) immunity to influenza virus, in 659 patients with life-threatening COVID-19 pneumonia, relative to 534 subjects with asymptomatic or benign infection. By testing these and other rare variants at these 13 loci, LOF variants were defined in 23 patients (3.5%), aged 17 to 77 years, underlying autosomal recessive or dominant deficiencies. Human fibroblasts with mutations affecting this pathway were shown to be vulnerable to SARS-CoV-2. A report by Bastard (Science 2020, see ***below***) further supported the role of type I IFN, as it described the presence of neutralizing auto-antibodies against type I in other patients with life-threatening COVID-19 pneumonia. At least 101 of 987 patients with life-threatening COVID-19 pneumonia had neutralizing IgG auto-Abs against IFN-ω (13 patients), the 13 types of IFN-α (36), or both (52), at the onset of critical disease; a few also had auto-Abs against the other three type I IFNs. The auto-Abs neutralize the ability of the corresponding type I IFNs to block SARS-CoV-2 infection in vitro. These auto-Abs were not found in 663 individuals with asymptomatic or mild SARS-CoV-2 infection and were present in only 4 of 1227 healthy individuals.

NK cells

NK cell count reduces remarkably during SARS-CoV-2 infection, predominantly in critically ill patients (Masselli Adv Biol Regul 2020, see ***below***). This is consistent with previous findings in SARS and it is conceivable that this finding is due to NK sequestration into target organs, e.g. the lung. However, it is unclear at this time if this decrease is due to NK cell redistribution in infected sites or cell death. In addition, a very interesting mechanism of T and NK cell exhaustion has been hypothesized by Zheng, Gao et al. (Cell Mol Imm 2020, see ***below***). In their work, the authors observed that the NK group 2 member A (NKG2A) receptor, which transduces inhibitory signalling and suppresses T-cell and NK cytokine secretion and cytotoxic function, is overexpressed in COVID-19 patients as compared to healthy controls, while the percentage of T and NK cells expressing the activation markers CD107a, IFNɣ, IL-2, and TNFα was significanly lower. Taken together, these data indicate that patients with severe COVID-19 have a severely compromised innate immune response likely due to a functional exhaustion of peripheral CD8+ T and NK cells.

Immune evasion mechanisms

As a member of the βCoV genus, SARS-CoV-2 can be expected to stimulate immune evasion mechanism potentially similar to those of SARS-CoV and MERS-CoV (Prompetchara Asia Pac J All Imm 2020, see ***below***). The mechanisms of how SARS-CoV and MERS-CoV modulate host immune responses were extensively studied. In brief, most mechanisms rely on the inhibition of innate immune responses, especially type I interferon recognition and signalling. The viral proteins including membrane (M) or nonstructural (NS) proteins (eg. NS4a, NS4b, NS15) are the key molecules in host immune modulation.

Type I interferon

Xia, Cao et al. (Cell Rep 2020, see ***below***) identified SARS-CoV-2 proteins that antagonize type I interferon (IFN-I) response: nsp6 binds TANK binding kinase 1 (TBK1) to suppress interferon regulatory factor 3 (IRF3) phosphorylation,

nsp13 binds and blocks TBK1 phosphorylation, and ORF6 binds importin Karyopherin α 2 (KPNA2) to inhibit IRF3 nuclear translocation. The authors identified two sets of viral proteins that antagonize IFN-I signalling through blocking signal transducer and activator of transcription 1 (STAT1)/STAT2 phosphorylation or nuclear translocation. Remarkably, SARS-CoV-2 nsp1 and nsp6 were found to suppress IFN-I signalling more efficiently than SARS-CoV and MERS-CoV.

Interferon stimulated genes

To identify the molecular effectors that govern interferon control of SARS-CoV-2 infection, Martin-Sancho (manuscript on bioRxiv, see ***below***) conducted a large-scale gain-of-function analysis that evaluated the impact of human interferon stimulated genes (ISGs) on viral replication. A limited subset of ISGs were found to control viral infection, including endosomal factors that inhibited viral entry, nucleic acid binding proteins that suppressed viral RNA synthesis, and a highly enriched cluster of ER and Golgi-resident ISGs that inhibited viral translation and egress. These included the type II integral membrane protein BST2/tetherin, which was found to impede viral release, and is targeted for immune evasion by SARS-CoV-2 Orf7a protein.

RNAi

As explained by Mu (Sci China Life Sci 2020, see ***below***), viral infection generates virus-derived dsRNA (vi-dsRNA), which could be recognized and cleaved by the host endoribonuclease Dicer into virus-derived siRNAs (vsiRNAs). These vsiRNAs are integrated into the Argonaute protein within the RNA-induced silencing complex (RISC) to direct the destruction of cognate viral RNAs in infected cells in a sequence-specific manner. As a countermeasure, viruses encode viral suppressors of RNAi (VSRs) to antagonize the RNAi pathway at different steps. Previous study has reported that SARS-CoV nucleocapsid (N) protein displayed a VSR activity in mammalian cells via a cellular reversal-of-silencing assay. Mu showed that SARS-CoV-2 can act as a VSR in cells in both initiation and effector steps of RNAi, thereby probably representing a key immune evasion factor of SARS-CoV-2 and contributing to the pathogenicity of the virus.

NKG2A expression and NK and CD8+ T cells

Zheng, Gao et al. (Cell Mol Imm 2020, see ***below***) showed that the total number of NK and CD8+ T cells was decreased markedly in patients with SARS-CoV-2 infection, and further observed that NKG2A expression is upregulated on NK cells and CTLs in patients, with a reduced ability to produce CD107a, IFN-γ, IL-2, granzyme B, and TNF-α. Also, the percentage of NKG2A+ cytotoxic lymphocytes was found decreased in recovered patients infected with SARS-CoV-2, which strongly suggests that **NKG2A expression** may be correlated with functional exhaustion of cytotoxic lymphocytes and disease progression in the early stage of COVID-19.

Clinical disease

Initial observations in Wuhan

In December, 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China, with clinical presentations greatly resembling viral pneumonia (http://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/). By Jan 2, 2020, 41 admitted hospital patients had been identified as having laboratory-confirmed COVID-19 (Huang Lancet 2020, see ***below***). Most of the infected patients were men (30 [73%] of 41); less than half had underlying diseases (13 [32%]), including diabetes (eight [20%]), hypertension (six [15%]), and cardiovascular disease (six [15%]). Median age was 49.0 years (IQR 41.0-58.0). 27 (66%) of 41 patients had been exposed to Huanan seafood market. One family cluster was found. Common symptoms at onset of illness were fever (40 [98%] of 41 patients), cough (31 [76%]), and myalgia or fatigue (18 [44%]); less common symptoms were sputum production (11 [28%] of 39), headache (three [8%] of 38), haemoptysis (two [5%] of 39), and diarrhoea (one [3%] of 38). Dyspnoea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnoea 8·0 days [IQR 5.0-13.0]). 26 (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT. Complications included acute respiratory distress syndrome (12 [29%]), RNAaemia (six [15%]), acute cardiac injury (five [12%]) and secondary

infection (four [10%]). 13 (32%) patients were admitted to an ICU and six (15%) died. Compared with non-ICU patients, ICU patients had higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα.

Incubation period

Among the first 425 patients with confirmed COVID-19-pneumonia, the mean incubation period was 5.2 days (95% confidence interval, 4.1 to 7.0), with the 95th percentile of the distribution at 12.5 days (Li New Engl J Med 2020, see ***below***). This observation was confirmed by other datasets as illustrated in ***Table 2*** below.

Table 2 Incubation period as reported by different studies

	Mean incubation period and 95% confidence interval	Other information
Li NewEngl J Med 2020	5.2 days (95% CI, 4.1 to 7.0)	95th percentile of the distribution at 12.5 days
Liu (https://www.biorxiv.org/content/10.1101/2020.01.25.919787v2)	4.8 days (±2.6)	ranging from 2 to 11 days
Wang (https://www.medrxiv.org/content/10.1101/2020.02.21.20026112v2)	7.4 days	median 7 days (no more than 14 days for 92% patients)
Backer EuroSurv 2020	6.4 days (95% CI, 5.6 - 7.7)	ranging from 2.1 to 11.1 days (2.5th to 97.5th percentile)
Guan NEJM 2020		median of 3 days; ranging from 0 to 24 days
Xu BMJ 2020		median 4 days (interquartile range 3-5 days)
Jia Disaster Med Public Health Prep 2020	6.28 days	
Leung Infect Control Hosp Epidemiol 2020	1.8 days (95% CI, 1.0 to 2.7)	For travellers to Hubei
Leung Infect Control Hosp Epidemiol 2020	7.2 days (95% CI, 6.1 to 8.4)	For non-travellers

Lauer (Ann Intern Med 2020, see ***below***) assessed the incubation period using a compilation of 181 published cases with identifiable exposure and symptom onset windows. A median incubation period of 5.1 days (95% CI, 4.5 to 5.8 days) was found, with 97.5% of those who develop symptoms doing so within 11.5 days (CI, 8.2 to 15.6 days) of infection. These estimates imply that, under conservative assumptions, 101 out of every 10,000 cases will develop symptoms after 14 days of active monitoring or quarantine. Whether this risk is acceptable will depend on the underlying risk of infection and consequences of missed cases.

Similar results were obtained by Linton (J Clin Med 2020 see ***below***), who found the incubation period to falls within the range of 2–14 days with 95% confidence and to have a mean of around 5 days. Based on the 95th percentile estimate of the incubation period, she recommended that the length of quarantine should be at least 14 days.

A systematic review of COVID-19 epidemiology by Park (J Clin Med 2020, see ***below***), which included 41 studies, indicated an estimated incubation period of 4-6 days.

Interestingly, based on reports collected in China, Han (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.24.20027474v1) found that the incubation periods of groups of individuals with age ≥40 years and age <40 years demonstrated a statistically significant difference. The former group had a longer incubation period and a larger variance than the latter. Cai (Clin Inf Dis 2020, see ***below***) reported an incubation period in children of about two days usually, with a range of 2-10 days.

Description of clinical disease

Shi (Cell Death Diff 2020, see ***below***) described SARS-CoV-2 infection as a 3-stage process: stage I, an asymptomatic incubation period with or without detectable virus; stage II, non-severe symptomatic period with the presence of virus; stage III, severe respiratory symptomatic stage with high viral load.

Clinical disease in China

Individual reports

A large number of reports provide descriptions of the clinical signs associated with COVID-19 in Wuhan and other cities in China. The disease ranges from mild infection to severe acute respiratory infection. ***Table 3*** illustrates the signs and symptoms detected in a selection of early reports describing the disease as observed in hospitalized patients.

Table 3 Clinical presentation in different cohorts of patients with COVID-19 pneumonia (frequency of reported symptoms)

	Chen Lancet 2020 (n=99*)	Song Radiol 2020 (n=51)	Chang JAMA 2020 (n=13)	Guan NEJM 2020 (n=1099**)	Wang JAMA 2020 (n=138)
fever	83%	96%	92.3%	88.7%	98.6%
cough	82%	47%	46.3%	67.8%	59.4%
shortness of breath (dyspnoea)	31%			18.7%	31.2%
muscle ache (myalgia)	11%	31%	23.1%	14.9%	34.8%
fatigue				38.1%	69.6%
confusion	9%				
headache	8%	16%	23.1%	13.6%	
sore throat	5%			13.9%	
rhinorrhoea	4%				
chest pain	2%				
diarrhoea	2%	10%		3.8%	10.1%
nausea and vomiting	1%			5%	10.1%
acute respiratory distress syndrome	17%			3.4%	

** Among the 99 patients, 76% patients received antiviral treatment, including oseltamivir (75 mg every 12 h, orally), ganciclovir (0.25 g every 12 h, intravenously), and lopinavir and ritonavir tablets (500 mg twice daily, orally). The duration of antiviral treatment was 3-14 days (median 3 days)*

*** Patients with laboratory-confirmed COVID-19 acute respiratory disease from 552 hospitals in 31 provinces/provincial municipalities through January 29th, 2020; see https://www.medrxiv.org/content/10.1101/2020.02.06.20020974v1*

Additional data were also made available in the reports listed below (non-exhaustive):

- Zhang (Virol Sin 2020, see ***below***) described 2 cases of COVID-19 in Wuhan
- Huang (Trav Med Inf Dis 2020, see ***below***) described 34 cases in Wuhan
- Chen (on MedRxiV: https://www.medrxiv.org/content/10.1101/2020.02.16.20023903v1) described 21 patients with COVID-19
- Li (on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.11.20022053v1) described 17 patients outside Wuhan
- Cai (on MedRXiv : https://www.medrxiv.org/content/10.1101/2020.02.17.20024018v1) described 298 confirmed cases in Shenzhen, from January 11, 2020 to February 6, 2020
- Zhang (Allergy 2020, see ***below***) described 140 patients in Wuhan, aged 25 to 87 years
- Liu (Chin Med J 2020, see ***below***) described 78 patients in Wuhan
- Yang (Lancet Resp Med 2020, see ***below***) described 52 critically ill patients
- Liu (on medRxiv https://www.medrxiv.org/content/10.1101/2020.02.17.20024166v3) described 109 patients, including 53 severe disease cases.
- Xu (BMJ 2020, see ***below***) described 62 hospitalized patients with confirmed infection in seven hospitals in Zhejiang province.
- Wu (Clin Inf Dis 2020, see ***below***) described 80 cases in Jiangsu Province.
- Yang (on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.28.20028068v1) analysed 55 hospitalized cases in Beijing.
- Zhou (Lancet 2020, see ***below***) provided details on 191 patients with laboratory-confirmed disease in Wuhan.
- Qian (QJM 2020, see ***below***) described 91 hospitalized patients with COVID-19 in Zhejiang.
- Lian (Influenza Other Respir Viruses 2020, see ***below***) analyzed 465 confirmed cases in Zhejiang province.

Metaanalyses

A meta-analysis by Sun (J Med Vir 2020, see ***below***below) covered ten of these studies[1], including a total number of 50 466 patients. It confirmed that fever and cough are the most common symptoms in patients with SARS-CoV-2 infection, and that a vast majority of these patients (96.6%) have abnormal chest CT examination. The incidence of fever was estimated at 89.1%, the incidence of cough 72.2%, and the incidence of muscle soreness or fatigue 42.5%. In this analysis, the incidence of acute respiratory distress syndrome (ARDS) reached 14.8%. ARDS is the most severe form of acute lung injury (Cheng, Wang et al. J Med Vir 2020, see ***below***). It is characterized mainly by increased pulmonary vascular permeability and pulmonary oedema. It is often induced by sepsis, aspiration, and pneumonia (including that caused by SARS coronavirus and human influenza viruses). It is a clinical, high-death-rate disease.

Diarrhoea, haemoptysis, headache, sore throat, shock, and other symptoms were reported to occur only in a small number of patients.

Of note, Sun (J Med Vir 2020, see ***below***) reported a definition of fever as temperature ≥ 37.3°C. He did not provide details on the method of temperature recording (e.g. axillary, forehead or sublingual). By contrast, Guan (NEJM 2020, see ***below***) mentioned a definition of fever as an axillary temperature of 37.5°C or higher. Such discrepancies can be expected to result in some variability across hospitals with regard to the detection of this symptom.

Another meta-analysis by Li (J Med Vir 2020, see ***below***), including a somewhat different set of ten studies[2] found the main clinical symptoms of COVID-19 patients to be fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (28.2%), and dyspnoea (21.9%). In addition to common respiratory symptoms, the symptoms of headache or dizziness (12.1%), diarrhoea (4.8%), nausea, and vomiting (3.9%) were also obvious in some patients.

A third meta-analysis by Rodriguez-Morales (Trav Med Inf Dis 2020, see ***below***) found that in 656 patients, fever (88.7%, 95%CI 84.5-92.9%), cough (57.6%, 40.8-74.4%) and dyspnea (45.6%, 10.9-80.4%) were the most prevalent manifestations. Among the patients, 20.3% (95%CI 10.0-30.6%) required intensive care unit (ICU), 32.8% presented with ARDS (95%CI 13.7-51.8), 6.2% (95%CI 3.1-9.3) with shock. Some 13.9% (95%CI 6.2-21.5%) of hospitalized patients had fatal outcome.

Borges do Nascimento (J Clin Med 2020, see ***below***) provided another meta-analysis of available clinical data, covering a total of 61 studies (59,254 patients). The most common disease-related symptoms were fever (82%, 95% confidence interval (CI) 56%–99%; n = 4410), cough (61%, 95% CI 39%–81%; n = 3985), muscle aches and/or fatigue (36%, 95% CI 18%–55%; n = 3778), dyspnoea (26%, 95% CI 12%–41%; n = 3700), headache in 12% (95% CI 4%–23%, n = 3598 patients), sore throat in 10% (95% CI 5%–17%, n = 1387) and gastrointestinal symptoms in 9% (95% CI 3%–17%, n = 1744).

A relevant feature of COVID-19, not addressed by the meta-analyses, is the absence of dyspnoea, observed even in the most severe cases, in which subjects present tachypnoea and tachycardia (Bertran Recasens Eur J Neurol 2020, see ***below***). In the Wuhan cohort, 62.4% of severe cases and 46.3% of those who ended up intubated, ventilated or dead did not present dyspnoea.

Less frequent observations

Hu (Eur Heart J, see ***below***) presented a COVID-19 case with fulminant myocarditis with cardiogenic shock. This clinical presentation had initially been reported to be rare, but was subsequently better recognized. A review by Bansal

[1] Huang Lancet 2020; Wang JAMA 2020 ; Chen Lancet 2020; Guan NEJM 2020 ; Chen Zhonghua Jie He He Hu Xi Za Zhi.; Sun, Lancet 2020; Yang medRxiv 2020 (manuscript subsequently withdrawn); Li medRxiv 2020; The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, Chinese Center for Disease Control and Prevention. Zhong Hua Liu Xing Bing Xue Za Zhi 2020; Xu BMJ 2020.

[2] Huang Lancet 2020; Chang JAMA 2020; Guan NEJM 2020; Wang JAMA 2020; Li N Engl J Med 2020; Chen Lancet 2020; Wang Biosci Trends 2020; Kui Chin Med J 2020; Lei Chin J Tuberc Resp Dis 2020; Mingqiang Chin Med J 2020.

(Diabetes Metab Syndr 2020, see ***below***) indicated that acute cardiac injury, defined as significant elevation of cardiac troponins, is the most commonly reported cardiac abnormality in COVID-19. It occurs in approximately 8-12% of all patients. Direct myocardial injury due to viral involvement of cardiomyocytes and the effect of systemic inflammation appear to be the most common mechanisms responsible for cardiac injury.

Of note, while expression of the ACE2 receptor in kidney and bladder had suggested the possibility of renal involvement in COVID-19, Wang (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.19.20025288v1) analysed data from 116 hospitalized patients, and concluded that acute renal impairment was uncommon in COVID-19, and that there was no aggravation of chronic renal failure observed in this cohort.

Although abnormalities of liver function indexes are common in COVID-19 patients, based on a retrospective study conducted on 115 confirmed cases, the impairment of liver function was not found by Zhang (Liver Int 2020, see ***below***) to be a prominent feature of COVID-19.

A report by Zhao (Lancet Neurol 2020, see ***below***) described a case of SARS-CoV-2 infection associated with Guillain-Barré syndrome.

Clinical disease outside China

Descriptions of cases that occurred outside China are also available. For instance:

- Ki (Epidemiol Health 2020, see ***below***) described the early cases identified in Korea,
- Holshue the first case in the United States of America (USA) (New Engl J Med 2020, see ***below***), and Harcourt (Emerg Infect Dis 2020, see ***below***) the virus isolation from this patients and its characterization,
- Arentz (JAMA 2020, see ***below***) 21 critically Ill patients with COVID-19 in Washington State, USA,
- Bastola (Lancet Inf Dis 2020, see ***below***) and Shrestha (J Travel Med 2020, see ***below***) the first case in Nepal,
- Silverstein (Lancet 2020, see ***below***) and Marchand-Senecal (Clin Inf Dis 2020, see ***below***) described the first imported case in Canada,
- Van Cuong (Lancet Inf Dis 2020, see ***below***) the first case in Vietnam,
- Cheng (J Formos Med Assoc 2020, see ***below***) described the first case in Taiwan, and Huang (J Micr Imm Inf 2020, see ***below***) 2 cases in Taiwan,
- Lillie (J Inf 2020, see ***below***) described 2 cases in the UK with person to person transmission,
- Young (JAMA 2020, see ***below***) described the case series of the first 18 patients with PCR-confirmed SARS-CoV-2 infection at 4 hospitals in Singapore from January 23 to February 3, 2020,
- The COVID-19 National Emergency Response Center (Osong Public Health Res Perspect 2020, see ***below***) presented 28 cases in South Korea,
- Bernard Stoecklin (Euro Surv 2020, see ***below***) and Lescure (Lancet Inf Dis 2020, see ***below***) presented the first cases in France,
- Pongpirul (Emerg Infect Dis. 2020, see ***below***) described 11 cases in Thailand,
- Goyal (NEJM 2020, see ***below***) described the key characteristics of 393 patients in New York.

Spiteri (Euro Surv 2020, see ***below***) described the first cases detected in Europe, excluding cases reported in the United Kingdom (UK), as at 21 February 2020. The analysis included both sporadic cases among travellers from China (14 cases) and cases who acquired infection due to subsequent local transmission in Europe (21 cases). The clinical presentation observed in the cases in Europe is that of an acute respiratory infection. However, of the 31 cases with information on symptoms, 20 cases presented with fever and nine cases presented only with fever and no other symptoms.

Tostmann (Euro Surv 2020, see ***below***) reported data from a Dutch study in which all 1247 HCW tested between 10 and 29 March 2020 received an email with a link to an online questionnaire on the symptoms they experienced before their test. Test-positive HCW most frequently reported headache (71%), general malaise (63%) and muscle ache (63%).

A systematic review by Grant (PLoS One 2020, see ***below***) determined the prevalence of symptoms associated with COVID-19 worldwide. The most prevalent symptoms were fever (78% [95% CI 75%-81%]; 138 studies, 21,701 patients; I2 94%), a cough (57% [95% CI 54%-60%]; 138 studies, 21682 patients; I2 94%) and fatigue (31% [95% CI 27%-35%]; 78 studies, 13,385 patients; I2 95%). Overall, 19% of hospitalised patients required non-invasive ventilation (44 studies, 6513 patients), 17% required intensive care (33 studies, 7504 patients), 9% required invasive ventilation (45 studies, 6933 patients) and 2% required extra-corporeal membrane oxygenation (12 studies, 1486 patients).

A Cochrane review undertaken on 27 April 2020 identified 16 studies including 7706 participants (Struyf Cochrane Database Syst Rev 2020, see ***below***). Prevalence of COVID-19 varied from 5% to 38% with a median of 17%. The authors found data on 27 signs and symptoms, falling into four different categories: systemic, respiratory, gastrointestinal and cardiovascular. No studies assessed combinations of different signs and symptoms and results were highly variable across studies. Most had very low sensitivity and high specificity; only six symptoms had a sensitivity of at least 50% in at least one study: cough, sore throat, fever, myalgia or arthralgia, fatigue, and headache. Of these, fever, myalgia or arthralgia, fatigue, and headache could be considered red flags (defined as having a positive likelihood ratio of at least 5) for COVID-19 as their specificity was above 90%, meaning that they substantially increase the likelihood of COVID-19 when present.

Non-respiratory symptoms

Cardiac manifestations

A meta-analysis by Li (Prog Cardiovasc Dis 2020, see ***below***), based on a systematic literature search across Pubmed, Embase and pre-print from December 1, 2019 to March 27, 2020, found acute cardiac injury more frequent in those with severe, compared to milder, disease (risk ratio 5.99, 3.04 to 11.80; $p < 0.001$). Meta-regression suggested that cardiac injury biomarker differences of severity are related to a history of hypertension ($p = 0.030$). In addition, COVID19-related cardiac injury was associated with higher mortality (summary risk ratio 3.85, 2.13 to 6.96; $p < 0.001$). hsTnI and NT-proBNP levels increased during the course of hospitalization only in non-survivors.

More recent reviews confirmed these observations. For instance, a narrative literature review by Cruz Rodriguez (J Invest Med, see ***below***) indicated that myocardial injury has been reported in 20%-30% of patients hospitalized due to COVID-19 and is associated with a worse prognosis and high mortality (~50%-60%). Proposed mechanisms of myocardial injury include inflammation within the myocardium (due to direct viral infection or cytokine storm), endotheliitis, coronary vasculitis, myocarditis, demand ischemia, plaque destabilization and right ventricular failure. The right ventricle is particularly vulnerable to injury and failure in COVID-19-infected patients, given the hypoxic pulmonary vasoconstriction, pulmonary microthrombi or pulmonary embolism.

Gastrointestinal symptoms

A U.S. case-control study among the 278 COVID-19 positive patients showed 35% of patients had gastrointestinal symptoms (Nobel Gastroenterology 2020, see ***below***)

Skin disorders

Searching for evidence of skin involvement of COVID-19, Recalcati (J Eur Acad Dermatol Venereol 2020, see ***below***) retrospectively analysed 88 patients, of which 18 patients (20.4%) developed cutaneous manifestations: 8 patients developed cutaneous involvement at the onset, 10 patients after the hospitalization. Cutaneous manifestations were erythematous rash (14 patients), widespread urticaria (3 patients) and chickenpox-like vesicles (1 patient). This was the first report of this kind. Joob (J Am Acad Dermatol 2020, see ***below***) also provided a case report from Thailand

where the patient presented a skin rash with petechiae. Other common virus infections that might cause fever, rash and respiratory problem were ruled out by laboratory investigation and the final diagnosis of COVID-19 infection was by RT-PCR.

Zulfiqar (NEJM 2020, see ***below***) described a case of thrombocytopenic purpura in a female patient with COVID-19. The temporal sequence in this case suggested, but did not prove, that COVID-19 was a causal factor.

Kolivras (JAAD Case Rep. 2020, see ***below***) presented a case report of COVID-19 induced chilblains. Other reports of such symptom had appeared before in social media and in scientific literature. This case was interesting as a punch biopsy was obtained. Histopathologic findings resembled chilblain lupus with an absence of significant papillary dermal oedema. There was a superficial and deep lymphoplasmacytic infiltrate.

Subsequent reports confirmed these observations, and various review papers were made available (see for instance Wollina (Dermatol Ther 2020, see ***below***). As recently summarized by Singh (Adv Wound Care New Rochelle 2020, see ***below***) cutaneous manifestations have been found in people of all age groups, including children. The cutaneous manifestations of COVID-19 are varied and include maculopapular, chilblain-like, urticarial, vesicular, livedoid, and petechial lesions. In addition, rashes are common in multisystem inflammatory syndrome in children, a new and serious health condition that shares symptoms with Kawasaki disease and is likely related to COVID-19. In addition, personal protective equipment-related skin wounds are of serious concern since broken cutaneous barriers can create an opening for potential COVID-19 infections.

Ocular manifestations

A recent systematic review and meta-analysis by Cao (Biomed Res Int 2020, see ***below***) included a total of 12 studies with 1930 participants. The pooled prevalence rate of conjunctivitis/conjunctival congestion was 8% (95% CI: 5%-12%). 1% (95% CI: 1%-4%) of COVID-19 patients were diagnosed with conjunctivitis/conjunctival congestion as the initial symptom. The pooled positive rate of conjunctival swab samples was 3% (95% CI: 2%-5%). The authors also assessed other ocular symptoms, including foreign body sensation, increased secretion, and eye itching. The pooled prevalence rates were 6% (95% CI: 3%-10%), 10% (95% CI: 8%-12%), and 9% (95% CI: 7%-10%), respectively.

Venous thromboembolism

While alterations of the coagulation pathways had soon been detected by clinical laboratory analyses, reports of thromboembolism related to COVID-19 appeared a few weeks later in the scientific literature.

- Davoodi (preprint available at Research Square: https://www.researchsquare.com/article/rs-21602/v1) reported a case of deep vein thrombosis in a 57-year-old woman presenting with pain, redness, and leg swelling, who was then diagnosed with COVID-19.
- Cui (J Thromb Haemost. 2020, see ***below***) found an incidence of 25% (20/81) venous thromboembolism among patients with severe disease; 8 of these patients with venous thromboembolism events died. The venous thromboembolism group was different from the non-venous thromboembolism group in age, lymphocytes counts, activated partial thromboplastin time (APTT), D-dimer, etc. If 1.5 μg/mL was used as the D-dimer cut-off value to predicting venous thromboembolism, the sensitivity was 85.0%, the specificity was 88.5% and the negative predictive value (NPV) was 94.7%.
- The incidence of thrombotic complications (composite outcome of symptomatic acute pulmonary embolism, deep-vein thrombosis, ischemic stroke, myocardial infarction or systemic arterial embolism) was studied in 184 ICU patients with proven COVID-19 pneumonia at 3 Dutch hospitals (Klok Thrombosis Res 2020: https://www.sciencedirect.com/science/article/pii/S0049384820301201). All patients received at least standard dose thromboprophylaxis. The cumulative incidence of the composite outcome was 31% (95%CI 20-41), of which CT pulmonary angiography and/or ultrasonography confirmed venous thromboembolismin 27% (95%CI 17-37%) and arterial thrombotic events in 3.7% (95%CI 0-8.2%). Acute pulmonary embolism was the

most frequent thrombotic complication (n = 25, 81%). In this study, age (adjusted hazard ratio (aHR) 1.05/per year, 95%CI 1.004-1.01) and coagulopathy, defined as spontaneous prolongation of the prothrombin time > 3 s or activated partial thromboplastin time > 5 s (aHR 4.1, 95%CI 1.9-9.1), were independent predictors of thrombotic complications.

- A retrospective study conducted in France evaluated 26 consecutive patients with severe COVID-19 (Llitjos J Thromb Haemost 2020, see ***below***). Eight of these patients (31%) were treated with prophylactic anticoagulation whereas 18 patients (69%) were treated with therapeutic anticoagulation. The overall rate of venous thromboembolic events in patients was 69%. The proportion of venous thromboembolic events was significantly higher in patients treated with prophylactic anticoagulation when compared to the other group (100% vs. 56%, respectively, p=0.03). Surprisingly, the authors found a high rate of thromboembolic events in COVID-19 patients treated with therapeutic anticoagulation, with 56% of venous thromboembolic events and 6 pulmonary embolisms.

Kermani-Alghoraishi (Curr Probl Cardiol 2020, see ***below***) reviewed venous thromboembolism phenomena in COVID-19 patients and the importance of their timely diagnosis. A systematic review by Divani (J Stroke Cerebrovasc Dis, see ***below***) provided more insights into the clinical manifestations and pathophysiological mechanisms of stroke in COVID-19 patients. SARS-CoV-2 can down-regulate ACE2 and, in turn, overactivate the classical renin-angiotensin system (RAS) axis and decrease the activation of the alternative RAS pathway in the brain. The consequent imbalance in vasodilation, neuroinflammation, oxidative stress, and thrombotic response may contribute to the pathophysiology of stroke during SARS-CoV-2 infection.

Neurological manifestations

A few months into the epidemic, Asadi-Pooya (J Neurol Sci 2020, see ***below***) found highly likely that some patients, particularly those who suffer from a severe illness, have CNS involvement and neurological manifestations, even though such evidence was scarce and of low quality. More solid data on this topic accumulated in the following months; the number of recognized neurologic manifestations of SARS-CoV-2 infection increased rapidly. These neurologic manifestations may result from a variety of mechanisms, including virus-induced hyperinflammatory and hypercoagulable states, direct virus infection of the CNS, and postinfectious immune mediated processes (Koralnik Ann Neurol 2020, see ***below***). Numerous review papers documented the various neurological symptoms and complications associated with the infection (see for instance Azim Cureus 2020, see ***below***; Paterson Brain 2020, see ***below***; Nepal Crit Care 2020, see ***below***; Correia Neurol Psychiatry Brain Res 2020, see ***below***; Almqvist Ann Clin Transl Neurol 2020, see ***below***). A recent meta-analysis by Chua (Brain Inj 2020, see below) based on 48 studies reported on 70 patients with 73 neurological manifestations. 39 (53.4%) patients had stroke, 18 (24.7%) had Guillain-Barré syndrome and variants, 11 (15.1%) had meningitis, encephalitis, encephalopathy, or myelitis, and five (6.8%) had seizures. They had a mean age of 61.9 ± 17.7 years (60.6% male). Neurological disease occurred 8.1 ± 6.8 days from initial symptoms. Average mortality rate was 17.8%. Stroke has a mortality rate of 25.6%. Olfactory and gustatory dysfunction occurred in 59.9% and 57.5%, respectively.

Taste and olfactory disorders

In March 2020, multiple reports in the media started to associate anosmia and dysgeusia with COVID-19 (see for instance, https://www.sciencealert.com/mild-covid-19-might-cause-a-lost-of-smell-or-taste; or https://edition.cnn.com/2020/03/23/health/coronavirus-symptoms-smell-intl/index.html). Giacomelli (Clin Inf Dis 2020, see ***below***) performed a cross-sectional survey of the prevalence of olfactory and taste disorders in the context of SARS-CoV-2 infection. Twenty (33.9%) reported at least one taste or olfactory disorder and 11 (18.6%) both. Twelve patients (20.3%) presented the symptoms before the hospital admission, whereas 8 (13.5%) experienced the symptoms during the hospital stay. Taste alterations were more frequently (91%) before hospitalization, whereas after hospitalization taste and olfactory alteration appeared with equal frequency. Mao (JAMA Neurol 2020, see ***below***)

reported hypogeusia in 12 [5.6%]) and hyposmia in 11 out of 214 patients [5.1%]). A study by Lechien (Eur Arch Otorhinolaryngol 2020, see ***below***) involved 417 mild-to-moderate COVID-19 patients. Face pain and nasal obstruction were the most disease-related otolaryngological symptoms in this cohort. 85.6% and 88.0% of patients reported olfactory and gustatory dysfunctions, respectively. There was a significant association between both disorders ($p < 0.001$). Olfactory dysfunction appeared before the other symptoms in 11.8% of cases. Among the 18.2% of patients without nasal obstruction or rhinorrhoea, 79.7% were hyposmic or anosmic. The early olfactory recovery rate was 44.0%. Females were significantly more affected by olfactory and gustatory dysfunctions than males ($p = 0.001$).

Eliezer (JAMA Otolaryngol Head Neck Surg 2020, see ***below***) presented a case where the main symptom expressed by the patient infected by SARS-CoV-2 was the sudden and complete loss of the olfactory function without nasal obstruction. CT scan of the nasal cavity that showed bilateral inflammatory obstruction of the olfactory clefts that was confirmed on magnetic resonance imaging of the nasal cavity. There were no anomalies of the olfactory bulbs and tracts. Similarly, Galougahi (Acad Radiol 2020, see ***below***) found normal olfactory bulb volume without abnormal signal intensity in the olfactory bulb and tract and no sign of nasal congestion by magnetic resonance. This finding is consistent with prior reports of SARS-CoV-induced anosmia, where olfactory bulb MRI similarly did not demonstrate abnormal findings. The authors suggested further investigations incl. longitudinal MRI both in the acute and in follow-up phases of the disease.

Of note, Gane (Rhinology 2020, see ***below***) reported a case characterized by sudden onset anosmia in a COVID-19 confirmed patient who did not develop any further symptoms. Based on a survey of 2428 patients reporting new onset anosmia during the COVID-19 pandemic, Hopkins (Rhinology 2020, see ***below***) concluded that 1 in 6 patients with recent onset anosmia reports this as an isolated symptom. COVID-19 testing was not performed in this study, but the authors recommended additional studies to further investigate the link between this symptom and the virus.

In a Stockholm, Sweden, hospital, where 19.1% of the medical staff (N=2149) were seropositive for SARS-CoV-2 (IgG antibodies, as tested by multiplex assay displaying 99.4% sensitivity and 99.1% specificity), the symptoms with the strongest correlation to seroprevalence were anosmia and ageusia, indicating that both disorders be included in screening guidance and in the recommendations of self-isolation to reduce further spread of SARS-CoV-2 (Rudberg Nature Comm 2020, see ***below***).

Spinato (JAMA 2020, see ***below***) found that an altered sense of smell or taste was more frequent among 105 women (72.4%; 95% CI, 62.8%-80.7%) than among 97 men (55.7%; 95% CI, 45.2%-65.8%; P = .02).

Menni (Nature Med 2020, see ***below***) investigated whether loss of smell and taste is specific to COVID-19 in 2 618 862 individuals who used an app-based symptom tracker. Among the 18 401 who had undergone a SARS-CoV-2 test, the proportion of participants who reported loss of smell and taste was higher in those with a positive test result (4668 of 7178 individuals; 65.03%) than in those with a negative test result (2436 of 11223 participants; 21.71%) (odds ratio = 6.74; 95% confidence interval = 6.31–7.21).

Encephalopathy and/or encephalitis

Encephalopathy and/or encephalitis are reported by an increasing number of studies (Almqvist Ann Clin Transl Neurol 2020, see ***below***). Nepal (Crit Care 2020, see ***below***) reviewed 6 cases of encephalitis reported from China, Switzerland, Japan, and from America. The age of the patients ranged from early 20s to late 60s. All of them had preceding symptoms of fever and cough followed by a rapidly deteriorating level of consciousness. Meningeal irritability in the form of nuchal rigidity, Kernig's, and Brudzinski's was reported in two out of the six cases. Where lumbar puncture was performed, it showed lymphocytic pleocytosis typical of a viral meningo-encephalitis. SARS-CoV-2 was detected in the cerebrospinal fluid (CSF) in only one Chinese patient and Japanese patient.

An observational case series from France reported on neurological complications in intensive care unit patients: 13/58 of patients (22%) presented with encephalopathic features (Almqvist Ann Clin Transl Neurol 2020, see ***below***). Brain MRI showed that 8/13 patients displayed leptomeningeal enhancement on post‐contrast T1‐weighted and fluid‐attenuated inversion recovery (FLAIR) sequences – a sign of leptomeningeal inflammation. Another French study found that 7/26 patients (27%) showed EEG/MRI changes suggestive of encephalopathy. Also, several cases of acute necrotizing encephalopathy (ANE) or posterior reversible encephalopathy syndrome (PRES) have been described. A Turkish study showed that 12/27 patients (44%) showed abnormalities on brain MRI with signs suggestive of ischemia or menigoencephalitis. Of note, only minimal evidence points to direct infection of neurons/glial cells by SARS-CoV-2 viral particles, as shown by mostly negative RT-PCR analyses from CSF. Nevertheless, CSF from a small subset of patients with encephalitic features did test positive for SARS-CoV-2 RNA.

Cases of COVID-19-associated acute disseminated encephalomyelitis (ADEM) have also been reported (see for instance Parsons (J Neurol 2020, see ***below***) or de Miranda Henriques-Souza (Neuroradiol 2020, see ***below***).

Guillain-Barre Syndrome

Toscano (NEJM 2020, see ***below***) examined five patients who had Guillain-Barré syndrome after the onset of COVID-19. The findings were generally consistent with an axonal variant of Guillain-Barré syndrome in three patients and with a demyelinating process in two patients. The authors reported that they could not determine whether severe deficits and axonal involvement are typical features of COVID-19–associated Guillain-Barré syndrome. An additional case observed in Iran was reported by Sedaghat (J Clin Neurosci 2020, see ***below***), and a case in the U.S.A. presented by Virani (IDCases 2020, see ***below***). Subsequently, a review by Brouwer (Brouwer Infez Med 2020, see ***below***) identified a total of 9 cases of Guillain-Barré syndrome. Two Guillain-Barré syndrome variants have also been described in a case series from Spain. Specifically, one case of Miller Fisher syndrome and one case of polyneuritis cranialis associated with COVID-19 was described (Nepal Crit Care 2020, see ***below***). A similar review of case reports by Carrillo-Larco (Wellcome Open Res 2020, see ***below***) identified 12 cases of Guillain-Barré syndrome and COVID-19; one was a Miller Fisher case. The age ranged between 23 and 77 years, and there were more men (9/102). Guillain-Barré symptoms started between 5 and 24 days after those of COVID-19. The protein levels in cerebrospinal fluid samples ranged between 40 and 193 mg/dl. None of the cerebrospinal fluid samples tested positive for COVID-19.

Acute myelitis

Several authors documented acute myelitis in COVID-19 patients. The first of these cases was a 66-year-old male, from Wuhan, with a 5-day history of fever, who was admitted to the hospital and found positive for SARS-CoV-2 (reviewed by Nepal Crit Care 2020, see ***below***). After a night of high fever, he developed bilateral weakness of his lower limbs, with urinary and bowel incontinence, rapidly progressing to flaccid lower extremity paralysis and paraesthesia and numbness below T10. Planters were down going bilaterally. A clinical diagnosis of post-infectious acute myelitis was made. He received treatment with ganciclovir, lopinavir/ritonavir, moxifloxacin, dexamethasone, IVIG, and mecobalamin. His bilateral lower extremity paralysis ultimately improved. Subsequent reports of acute myelitis associated with COVID-19 included those by AlKetbi (Radiol Case Rep 2020, see ***below***), Durrani (Clin Pract Cases Emerg Med 2020, see ***below***), Sotoca (Neurol Neuroimmunol Neuroinflamm. 2020, see ***below***) and Águila-Gordo (J Clin Neurosci 2020, see ***below***).

Chow (BMJ Case Rep 2020, see ***below***), Chakraborty (BMJ Case Rep 2020, see ***below***) and Munz (J Neurol 2020, see ***below***) described cases of acute transverse myelitis. A case of acute necrotizing myelitis (ANM) and acute motor axonal neuropathy (AMAN), a rare variant of Guillain-Barré syndrome, was also described by Maideniuc (J Neurol 2020, see ***below***).

Clinical imaging

Chest computed tomography

A number of early reports provided a detailed description of chest computed tomography (CT) scan findings of patients with COVID-19 pneumonia. For instance:

- Kong Radiol 2020 (https://pubs.rsna.org/doi/full/10.1148/ryct.2020200028);
- Li Radiol 2020 (https://pubs.rsna.org/doi/full/10.1148/ryct.2020200026);
- Ng Radiol 2020 (https://pubs.rsna.org/doi/full/10.1148/ryct.2020200034);
- Song Radiol 2020, see ***below;***
- Chung Radiol 2020, see ***below***;
- Bernheim Radiol 2020, see ***below;***
- Yoon Korean J Radiol 2020, see ***below;***
- Xu Eur J Nucl Med Mol Imaging 2020, see ***below***;
- Yang (J Inf 2020, see ***below***) presented clinical imaging data from 149 RT-PCR confirmed positive patients in three tertiary hospitals of Wenzhou;
- Shi Lancet Inf Dis 2020, see ***below***;
- Xu (J Inf 2020, see ***below***) described data from 50 patients, including mild type, common, severe and critically severe cases;
- Albarello (Int J Infect Dis 2020, see ***below***) presented the CT findings in 2 cases in Italy;
- Li and Xia (AJR Am J Roentgenol 2020, see ***below***) described 51 cases in Wuhan;
- Zhou (AJR Am J Roentgenol 2020, see ***below***) described CT findings in 62 patients in Wuhan;
- Xiong (Invest Radiol 2020, see ***below***) described 42 cases in Wuhan including cases with progressive disease features;
- Zhu (J Inf 2020, see ***below***) described 6 cases in Guangzhou;
- Li (Ped Radiol 2020, see ***below***) presented CT findings from 5 children at a large tertiary-care hospital in China with positive RT-PCR for COVID-19;
- Xia (Pedriatr Pulmonol 2020, see ***below***) described 20 paediatric patients , of which 6 presented with unilateral pulmonary lesions (6/20, 30%), 10 with bilateral pulmonary lesions (10/20, 50%), and 4 showed no abnormality on chest CT (4/20, 20%);
- Zhao (Clin Radiol 2020, see ***below***) presented chest CT images of 80 patients in China.

Guan (NEJM 2020, see ***below***) found that on admission ground-glass opacity (see ***Figure 8***) was the typical radiological finding on chest CT (50.00%, in a dataset of 1 099 patients with laboratory-confirmed disease). The typical radiological imaging of COVID-19 pneumonia demonstrated destruction of the pulmonary parenchyma including interstitial inflammation and extensive consolidation, similar to SARS (Pan Radiol 2020, see ***below***). However, some patients with COVID-19 pneumonia consistently demonstrated no hypoxemia or respiratory distress during the course of hospitalization. A study in 21 patients recovering from COVID-19 pneumonia (without severe respiratory distress during the disease course) showed that lung abnormalities on chest CT showed greatest severity approximately 10 days after initial onset of symptoms. Dai (Can Assoc Radiol 2020, see ***below***) also discussed the difference between COVID-19 and other lung diseases.

Zhang (Int Care Med 2020, see ***below***) observed white “Septal Lines” in a 75-year-old male confirmed with severe COVID-19 pneumonia, suggesting that cellulosic exudation occurred at the surface of lung lobes.

Figure 8 CT lung imaging from a 41-year-old woman who tested positive for COVID-19. This 3-D reconstruction shows multifocal ground glass opacities without consolidation (from https://www.itnonline.com/content/radiologists-describe-coronavirus-ct-imaging-features).

Salehi (AJR Am J Roentgenol 2020, see ***below***) published a systematic review of imaging findings in 919 patients. The authors found the characteristic patterns and distribution of CT manifestations: ground glass opacification (GGO) (88.0%), bilateral involvement (87.5%), peripheral distribution (76.0%), and multilobar (more than one lobe) involvement (78.8%) (***Table 4***). Isolated GGO or a combination of GGO and consolidative opacities were some of the most common CT findings. Other CT findings included interlobular septal thickening, bronchiectasis, pleural thickening, and subpleural involvement, with various rates across the studies. Pleural effusion, pericardial effusion, lymphadenopathy, cavitation, CT halo sign, and pneumothorax were less common or rare.

Table 4 Common Patterns and Distribution on Initial CT Images of 919 Patients With COVID-19 (from Salehi AJR AM J Roentgenol 2020)

Imaging Finding	No. of Studies	No. (%) of Reported Cases/ Total No. of Patients
Bilateral involvement	12	435/497 (87.5)
Peripheral distribution	12	92/121 (76.0)
Posterior involvement	1	41/51 (80.4)
Multilobar involvement	5	108/137 (78.8)
Ground-glass opacification	22	346/393 (88.0)
Consolidation	10	65/204 (31.8)

Thirteen studies (2738 participants, with 2386 having abnormal CT imaging features) were included in a meta-analysis by Bao (J Am Coll Radiol, see ***below***), which was aimed at providing a more precise estimate of detection of COVID-19 by chest CT and reporting on the most common imaging findings on chest CT imaging. The pooled positive rate of the CT imaging was 89.76% and 90.35% when only including thin-section chest CT. Typical CT signs were ground glass opacities (83.31%), ground glass opacities with mixed consolidation (58.42%), adjacent pleura thickening (52.46%), interlobular septal thickening (48.46%), and air bronchograms (46.46%). Other CT signs included crazy paving pattern (14.81%), pleural effusion (5.88%), bronchiectasis (5.42%), pericardial effusion (4.55%), and lymphadenopathy (3.38%). The most anatomic distributions were bilateral lung infection (78.2%) and peripheral distribution (76.95%). The incidences were highest in the right lower lobe (87.21%), left lower lobe (81.41%), and bilateral lower lobes (65.22%). The right upper lobe (65.22%), right middle lobe (54.95%), and left upper lobe (69.43%) were also commonly involved. The incidence of bilateral upper lobes was 60.87%. A considerable proportion of patients had three or more lobes involved (70.81%).

Qin (Eur J Nucl Med Mol Imaging 2020, see ***below***) described for the first time the 18F-FDG PET/CT findings of four patients with COVID-19. The data confirmed previous observations of peripheral ground-glass opacities and/or lung consolidations (in more than two pulmonary lobes). Lung lesions were characterized by a high 18F-FDG uptake and there was evidence of lymph node involvement. Conversely, disseminated disease was absent, a finding suggesting that COVID-19 has pulmonary tropism.

Following the evaluation of 80 patients, Wu (Invest Radiol 2020, see ***below***) suggested significant correlations between the degree of pulmonary inflammation and the main clinical symptoms and laboratory results. Similarly, Zhao (AJR Am J Roentgenol 2020, see ***below***) investigated the relationship between chest CT findings and the clinical condition of 101 patients with COVID-19 pneumonia in Hunan, China, and found that architectural distortion, traction bronchiectasis, and CT involvement score aided in the evaluation of the severity and extent of the disease.

Based on a retrospective analysis of 27 consecutive patients, Yuan (PLoS One 2020, see ***below***) found that a simple CT scoring method was able to predict mortality.

Lung ultrasound

Chest CT has thus acquired a pivotal role for the diagnosis and assessment of lung involvement in COVID-19, and CT protocols are used to estimate the pulmonary damage. Unfortunately, CT scanning is not available in all emergency departments. Lung ultrasound is a surface imaging technique greatly developed in the last decades and strongly recommended for acute respiratory failure. Poggiali (Radiol 2020, see ***below***) presented preliminary data from 12 patients suggesting the feasibility of using bedside ultrasound for the early diagnosis of COVID-19 pneumonia. A recommendation for more studies on this topic was also made by Soldati (J Ultrasound Med 2020, see ***below***), who presented data from 2 additional cases. However, a study by Lu (Ultraschall Med 2020, see ***below***) showed moderate agreement (Kappa = 0.529) between bedside ultrasound for lung lesions and CT in patients with COVID-19. The ultrasound scores to evaluate mild, moderate and severe lung lesions exhibited sensitivity of 68.8% (11/16), 77.8% (7/9), 100.0% (2/2), specificity of 85.7% (12/14), 76.2% (16/21), 92.9% (26/28), and diagnostic accuracy of 76.7% (23/30), 76.7% (23/30), 93.3% (28/30), respectively.

A standardized approach has been proposed to optimize the use of lung ultrasound in COVID-19 patients (Soldati, Smargiassi et al. J Ultrasound Med 2020, see ***below***). Moreover, a panel of international experts evaluated the position of ultrasound in the management of COVID-19 and summarized benefits, open questions and challenges in the setting of the COVID-19 epidemic (Ultraschall Med 2020, see ***below***).

Laboratory finding & biomarkers

A number of reports present the laboratory observations associated with COVID-19. Various studies addressed the search for a prognostic marker of severe infection, while others focused on understanding pathological mechanisms.

Virus shedding & virus load

A large number of studies analysed the virus load in respiratory secretions of COVID-19 patients (mostly using RT-PCR). Key findings related to virus detection in patients are illustrated below.

Virus load and infectivity

The correlation of RNA-based viral load in the respiratory tract with infectivity, as measured in cell culture, even though limited, has been established by several studies. Wölfel (Nature 2020, see ***below***) provided a detailed virological analysis of 9 COVID-19 cases in Germany. Pharyngeal virus shedding was very high during the first week of symptoms (peak at 7.11×10^8 RNA copies per throat swab, day 4). Infectious virus was readily isolated from throat- and lung-derived samples, but not from stool samples, in spite of high virus RNA concentration. Blood and urine never yielded

virus. Active replication in the throat was confirmed by viral replicative RNA intermediates in throat samples. Sequence-distinct virus populations were consistently detected in throat and lung samples from the same patient, proving independent replication.

Virus load and disease severity

The viral load detected from the respiratory tract of patients was soon positively linked to lung disease severity (Liu Sci China Life Sci 2020, see ***below***), and subsequent studies confirmed this observation. Liu (Lancet Inf Dis 2020, see ***below***) presented data from 76 patients suggesting that the viral load of SARS-CoV-2 might be a useful marker for assessing disease severity and prognosis. The mean viral load of severe cases was indeed around 60 times higher than that of mild cases. However, Lescure (Lancet Inf Dis 2020, see ***below***) observed high nasopharyngeal virus load within the first 24 h of illness onset (5.2 and 7.4 log10 copies per 1000 cells, respectively), in 2 patients with few symptoms.

Virus load by age

Older age was correlated with higher viral load (Spearman's ρ=0·48, 95% CI 0·074-0·75; p=0·020) in a study by To (Lancet inf Dis 2020, see ***below***), but a study by Zhou (Clin Infect Dis 2020, see ***below***) did not reach the same conclusion when comparing patients <65 yrs [31.0 (IQR: 23.5-40.5) days] to those ≥65 yrs [31.0 (IQR: 24.3-38.0) days)].

Various studies also investigated the virus load in paediatric cases of infection. For instance, in a cohort of patients with mild to moderate illness within 1 week of symptom onset, Heald-Sargent (JAMA Ped 2020, see ***below***) compared 3 groups: young children younger than 5 years (n = 46), older children aged 5 to 17 years (n = 51), and adults aged 18 to 65 years (n = 48). The authors found similar median (interquartile range) CT values for older children (11.1 [6.3-15.7]) and adults (11.0 [6.9-17.5]). However, young children had significantly lower median (interquartile range) CT values (6.5 [4.8-12.0]), indicating that young children have equivalent or more viral nucleic acid in their upper respiratory tract compared with older children and adults. The topic was also addressed by Jones (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.06.08.20125484v1). In this study, viral loads of at least 250 000 copies, a threshold previously established by the authors for the isolation of infectious virus in cell culture at more than 5% probability, were present across the study period in 29.0% of kindergarten-aged patients 0-6 years old (n=38), 37.3% of those aged 0-19 (n=150), and in 51.4% of those aged 20 and above (n=3153). The authors concluded that a considerable percentage of infected people in all age groups, including those who are pre- or mild-symptomatic, carry viral loads likely to represent infectivity.

Virus load in different types of specimens

Presence of the virus in different types of clinical specimens was also analysed. Pan (Lancet Inf Dis 2020, see ***below***) for instance, reported such analysis from 82 infected individuals. The data can be summarized as follows:

- In 2 patients monitored daily, the viral loads in throat swab and sputum samples peaked at around 5-6 days after symptom onset, ranging from around 10^4 to 10^7 copies per mL during this time.
- In individuals at different stages of infection, viral loads ranged from 641 copies per mL to 1.34×10^{11} copies per mL, with a median of 7.99×10^4 in throat samples and 7.52×10^5 in sputum samples.
- A sputum sample collected on day 8 post-onset from a patient who died had a very high viral load ($1{\cdot}34 \times 10^{11}$ copies per mL).
- Notably, two individuals, who were under active surveillance because of a history of exposure to infected patients showed positive results on RT-PCR a day before onset, suggesting that infected individuals can be infectious before them become symptomatic.
- From 17 confirmed cases with available data (representing days 0–13 after onset), stool samples from nine (53%; days 0–11 after onset) were positive on RT-PCR analysis, but with lower viral loads than respiratory samples.

Another study by Chen, Lan et al. (Em Micr Inf 2020, see ***below***) found detectable SARS-CoV-2 RNA in the blood of 6 of 57 patients. Importantly, all of these 6 patients progressed to severe symptom stage, indicating a strong correlation of serum viral RNA with disease severity (p-value = 0.0001).

Kinetic studies

SARS-CoV-2 shedding kinetics has significant implications for hospital infection prevention and control, discharge management, and public health. Various early reports describing cases observed in China therefore covered this important topic. In the cohort of 191 patients with laboratory-confirmed disease described by Zhou (Lancet 2020, see ***below***), duration of viral shedding ranged between 8 and 37 days. The median duration of viral shedding was 20·0 days (IQR 17·0–24·0) in survivors, but continued until death in fatal cases.

In the study by Liu (Lancet Inf Dis 2020, see ***below***), the viral load of severe cases remained significantly higher for the first 12 days after onset than those of corresponding mild cases. Mild cases were also found to have an early viral clearance, with 90% of these patients repeatedly testing negative on RT-PCR by day 10 post-onset. By contrast, all severe cases still tested positive at or beyond day 10 post-onset.

From a small series of 8 patients with mild to moderate disease, Ma (J Microbiol Immunol Infect 2020, see ***below***) suggested that stool specimens of children may remain PCR-positive for a longer time than those of adults.

Chang (Am J Respir Crit Care Med 2020, see ***below***) determined the time kinetics of viral clearance in reference to the resolution of symptoms in 16 patients treated in Beijing, China, and showed that half of the patients with COVID-19 were viral positive even after resolution of their symptoms.

A study by To (Lancet inf Dis 2020, see ***below***) in 23 patients with COVID-19 showed a median viral load in posterior oropharyngeal saliva or other respiratory specimens at presentation of 5·2 log10 copies per mL (IQR 4·1-7·0). Salivary viral load was highest during the first week after symptom onset and subsequently declined with time (slope -0·15, 95% CI -0·19 to -0·11; R2=0·71). In one patient, viral RNA was detected 25 days after symptom onset.

Yuan (Inflamm Res 2020, see ***below***) presented a kinetic view of viral load, cell count and biochemical parameters in patients with mild/moderate and severe disease. The authors also observed that COVID-19 mRNA clearance ratio was significantly correlated with the decline of serum creatine kinase (CK) and lactate dehydrogenase (LDH) levels, which may then predict a favourable response to treatment.

Additional data were reported by Perera (Em Inf Dis 2020, see ***below***), who investigated 68 respiratory specimens from 35 coronavirus disease patients in Hong Kong, of whom 32 had mild disease. Culturable SARS-CoV-2 and subgenomic RNA were rarely detectable beyond 8 days after onset of illness. By contrast, virus RNA was detectable for many weeks by reverse transcription PCR.

Wölfel (Nature 2020, see ***below***) provided a detailed virological analysis of 9 COVID-19 cases in Germany. Pharyngeal virus shedding was very high during the first week of symptoms (peak at 7.11×10^8 RNA copies per throat swab, day 4). Shedding of viral RNA from sputum outlasted the end of symptoms. Of note, seroconversion occurred after 7 days in 50% of these patients (14 days in all), but was not followed by a rapid decline in viral load.

Fontana (Inf Contr Hosp Epi 2020, see ***below***) provided a review of available data on October 20 2020. Seventy-seven studies on SARS-CoV-2 were included. All studies reported PCR-based testing and 12 also included viral culture data. The overall pooled median duration of RNA shedding from respiratory sources was 18.4 days (95% CI: 15.5 days - 21.3 days; I2=98.87%, p<0.01) among 28 studies. When stratified by disease severity, the pooled median duration of viral RNA shedding from respiratory sources was 19.8 days (95% CI: 16.2 days – 23.5 days; I2=96.42%, p<0.01) among severely ill patients and 17.2 days (95% CI: 14.0 days - 20.5 days; I2=95.64%, p<0.01) in mild/moderate illness. Viral

RNA was detected up to 92 days after symptom onset. Viable virus was isolated by culture from -6 days to 20 days relative to symptom onset. The authors concluded that SARS-COV-2 RNA shedding can be prolonged, even though high heterogeneity has been observed. Detection of viral RNA may not correlate with infectivity since available viral culture data suggested shorter durations of shedding of viable virus. Additional data is still needed to determine the duration of shedding of viable virus and the implications for risk of transmission.

Cell counts

Various early reports characterized the changes in cell counts in COVID-19 patients. Among these publications, a manuscript by Liu (on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.10.20021584v1) based on the monitoring of 61 patients suggested the **neutrophil/lymphocyte ratio** as a predictive marker of severe illness. This biomarker proved superior to the MuLBSTA score that had been suggested before for COVID-19 patients monitoring. A subsequent report from data in 40 patients confirmed this conclusion (Liu EBioMed 2020, see ***below***).

Chen (J Clin Invest 2020, see ***below***) reported significantly lower **lymphocyte counts** in severe cases (0.7 × 109 125 /L) than moderate cases (1.1 × 109/L). Absolute number of T lymphocytes, CD4+T and CD8+T cells decreased in nearly all the patients, and were markedly lower in severe cases (294.0, 177.5 and 89.0 × 10^6/L) than moderate cases (640.5, 381.5 and 254.0 × 10^6/L). The expressions of IFN-γ by CD4+T cells tended to be lower in severe cases (14.1%) than moderate cases (22.8%).

A study by Zheng (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.19.20024885v1)

investigated differences in laboratory parameters between 103 COVID-19 and 22 non-COVID-19 pneumonia cases. The lymphocyte subsets counts were found to exhibit a significant negative correlation with biochemical indices relating to organ injury in the COVID-19 infected patients.

Similarly, Zeng (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.03.08.20031229v2) described a phenomenon of lymphocyte depletion (PLD) observed in 100% severe or critical cases (ICU). As the disease progressed and clinical status deteriorated, levels of lymphocytes were found progressively decreased before death.

A study by Tan (Signal Transduct Target Ther 2020, see ***below***) confirmed the observation of lymphopenia. Lymphocyte counts in severe patients were found to decrease initially and then increase to higher than 10% until discharge. In contrast, the lymphocyte count of moderate patients fluctuated very little after disease onset and was higher than 20% upon discharge. These results suggest that lymphopenia is a predictor of prognosis in COVID-19 patients.

Based on the observation that **eosinopenia** is frequently observed in COVID-19 patients (79% in SARS-CoV-2 positive patients vs. 36% in SARS-CoV-2 negative patients, Li (on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.13.20022830v1) suggested an alternative, simple, approach to facilitate triage of patients. The approach led to a diagnosis sensitivity and specificity of 79% and 64%, respectively. Zhang (Allergy 2020, see ***below***) also reported eosinopenia in most patients, but the frequency of the observation (52.9%) does not support the diagnostic value of this marker.

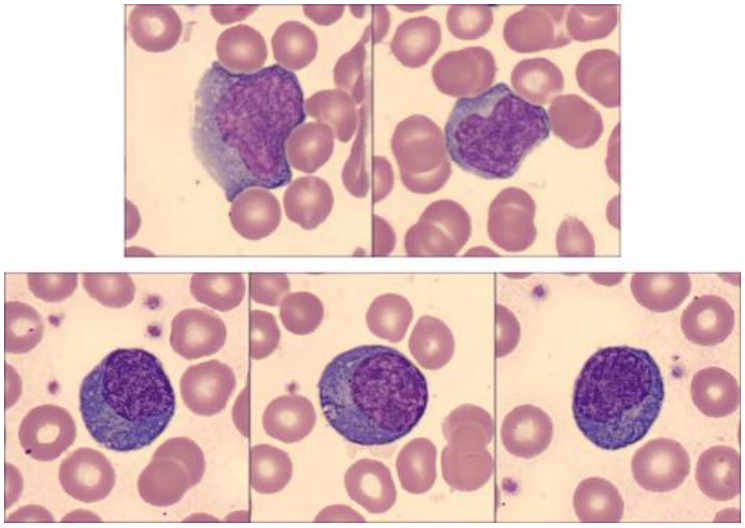
Qin (Clin Inf Dis 2020, see ***below***) described 452 patients who underwent laboratory examinations on admission. Similar to previous reports, the authors reported that severe cases tend to have lower lymphocytes counts, higher leukocytes counts and neutrophil-lymphocyte-ratio (NLR), as well as lower percentages of monocytes, eosinophils, and basophils. Most of severe cases demonstrated elevated levels of infection-related biomarkers and inflammatory cytokines. Lymphocyte subsets were analyzed in 44 patients with COVID-19 on admission. The total number of B cells, T cells and NK cells were significantly decreased in patients with COVID-19, and particularly in severe cases. The

percentage of naïve helper T cells (CD3+CD4+CD45RA+) increased and memory helper T cells (CD3+CD4+CD45RO+) were found decreased in severe cases.

Chong (Br J Haematol 2020, see ***below***) found reactive lymphocytes in 23/32 confirmed COVID-19 cases (72%) (***Figure 9***). This is in stark contrast to the 2003 SARS where reactive lymphocytes of this type were not present in a review of 185 cases in Singapore and were present in only 15.2% of 138 cases in Hong Kong.

Similarly, Foldes (Am J Hematol 2020, see ***below***) reported atypical lymphocytes that appeared reactive in a patient. Prominent among these were lymphoplasmacytoid lymphocytes with an eccentric nucleus, deeply basophilic cytoplasm and a prominent paranuclear hof.

Figure 9 Reactive lymphocyte in COVID-19 patients (from Chong Br J Haematol 2020)



The most common reactive lymphocyte subtype seen in COVID-19 patients displayed a distinctive abundant pale blue cytoplasm that often abuts adjacent red blood cells (top left and right). Lymphoplasmacytoid lymphocytes were present in 16 out of 23 patients (bottom images: left, right and centre).

Biochemistry

Elevated C-reactive protein (**CRP**) is an important feature of COVID-19 (Zhang Lancet Resp Med 2020, see ***below***). A study in 12 patients (Liu Sci China Life Sci 2020, see ***below***) found blood biochemistry indexes, albumin (ALB), CRP, lactate dehydrogenase (LDH), may be predictors of disease severity. Similarly, Liu (Chin Med J 2020, see ***below***) found CRP to be significantly elevated in a progression group compared to another group of patients with improvement/stabilization (38.9 [14.3, 64.8] vs. 10.6 [1.9, 33.1] mg/L, U = 1.315, P = 0.024). Albumin was significantly lower in the progression group than in the improvement/stabilization group (36.62 ± 6.60 vs. 41.27 ± 4.55 g/L, U = 2.843, P = 0.006).

In a cohort of 132 COVID-19 patients, Li (J Infect 2020, see ***below***) observed significantly increased serum amyloid A (**SAA**) and CRP levels. As disease progressed from mild to critically severe, SAA and CRP gradually increased, while lymphocyte counts decreased; a ROC curve analysis suggested that SAA/lymphocyte counts, CRP, SAA, and lymphocyte counts are valuable in evaluating the severity of COVID-19 and distinguishing critically ill patients from mild ones; patients with SAA consistently trending down during the course of disease had better prognosis, compared with patients with SAA continuously rising. Patient with higher initial SAA level were also more likely to have poor CT imaging.

Fan (Clin Gastroenterol Hepatol 2020, see ***below***) described a cohort of 148 patients, of which (50.7%) showed abnormal **liver function** at admission, characterized by increased ALT, AST, GGT, AKP.

Alanine aminotransferase, LDH levels, high-sensitivity CRP and ferritin were significantly higher in severe cases (41.4 U/L, 567.2 U/L, 135.2 mg/L and 1734.4 ug/L) than moderate cases (17.6 U/L, 234.4 U/L, 51.4 mg/L and 880.2 ug /L) (Chen on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.16.20023903v1). IL-2R, TNF-α and IL-10 concentrations on admission were significantly higher in severe cases (1202.4 pg/mL, 10.9 pg/mL and 10.9 pg/mL) than moderate cases (441.7 pg/mL, 7.5 pg/mL and 6.6 pg/mL).

Moreover, the **angiotensin II** level in the plasma sample from COVID-19 patients has been found markedly elevated and linearly associated to viral load and lung injury (Liu Sci China Life Sci 2020, see ***below***).

A meta-analysis by Lippi (Clin Chim Acta 2020, see ***below***) showed that increased **procalcitonin** values are associated with a nearly 5-fold higher risk of severe SARS-CoV-2 infection (OR, 4.76; 95% CI, 2.74-8.29). The heterogeneity among the different studies was found to be modest (i.e., 34%). As the synthesis of this biomarker is inhibited by INF-γ, whose concentration is expected to increase during viral infections, the authors speculate that increased procalcitonin could reflect bacterial superinfection in severe disease cases. However, more investigations are still needed to identify the origin of the biomarker.

Another meta-analysis by Lippi (Prog Cardiovasc Dis 2020, see ***below***) assessed **cardiac troponin I** (cTnI) in patients with COVID-19. Although the heterogeneity was considerably high, the values of cTnI were found to be significantly increased in patients with severe disease than in those without (SMD, 25.6 ng/L; 95% CI, 6.8–44.5 ng/L).

A meta-analysis by Henry (Clin Chem Lab Med. 2020, see ***below***) identified IL-6, IL-10 and serum ferritin as strong discriminators for severe disease.

Aziz (J Med Virol 2020, see ***below***) evaluated **IL6** as a marker of severe disease. A total of 9 studies were included in the systematic review and meta-analysis. Patients with severe COVID-19 had significantly higher serum IL-6 levels compared to non-severe patients (mean difference (MD): 38.6 pg/mL, 95% CI: 24.3 - 52.9 pg/mL, p <0.001, I2 = 98.5%). On meta-regression, increasing mean IL-6 level was associated with increased mortality in patients (Coefficient (Q): 0.01, 95% CI: 0.01-0.03, p = 0.03).

A nice review by Terpos (Am J Hematol 2020, see ***below***) provided a clear picture of the laboratory findings associated with COVID-19. Evidence was presented to support that various parameters have potential as predictive parameters for severity: lymphopenia, thrombocytopenia and neutrophilia (raised neutrophils) not only predict ARDS, but also cardiovascular complications. Raised procalcitonin, ferritin, LDH, IL-6 and CRP and the coagulation disorders (D-dimer, increased fibrin degradation, PTT and aPT) were also highlighted.

Coagulation parameters

Tang (J Thromb Haemost 2020, see ***below***) described the coagulation data of 183 consecutive patients with confirmed COVID-19 pneumonia. The non-survivors revealed significantly higher D-dimer and fibrin degradation product (FDP) levels, longer prothrombin time and activated partial thromboplastin time compared to survivors on admission (P<0.05). 71.4% of non-survivors and 0.6% survivors met the criteria of disseminated intravascular coagulation during their hospital stay.

Zhou (Lancet 2020, see ***below***) found increasing odds of in-hospital death associated with **D-dimer** levels greater than 1·0 µg/L (18·42, 2·64–128·55; p=0·0033) on admission. Gao (J Med Vir 2020, see ***below***) found that IL-6 and D-Dimer were closely related to the occurrence of severe COVID-19 in adult patients, and their combined detection had the

highest specificity and sensitivity for early prediction of the severity of disease. In this study in 43 patients, the specificity of predicting the severity of COVID-19 during IL-6 and D-Dimer tandem testing was up to 93.3%, while the sensitivity of such testing reached 96.4%.

A meta-analysis by Lippi (Clin Chim Acta 2020, see ***below***) included 1779 COVID-19 patients, of whom 399 (22.4%) had severe disease. The pooled analysis revealed that platelet count was significantly lower in patients with more severe COVID-19 (WMD -31×10^9/L; 95% CI, from -35 to -29×10^9/L). A subgroup analysis comparing patients by survival, found an even lower platelet count observed with mortality (WMD, -48×10^9/L; 95% CI, -57 to -39×10^9/L. In the four studies which reported data on rate of **thrombocytopenia** (n=1427), a low platelet count was associated with over five-fold enhanced risk of severe COVID-19 (OR, 5.1; 95% CI, 1.8-14.6).

Time from illness onset to death

In an analysis of early published data, Linton (J Clin Med 2020, see ***below***) found a median time delay of 13 days from illness onset to death (17 days with right truncation). However, the WHO-China Joint Mission on Coronavirus Disease 2019 Mortality, which analysed data on 2114 COVID-19 related deaths among 55 924 laboratory-confirmed cases in China, reported that the time between symptom onset and death ranged from about 2 weeks to 8 weeks (https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf).

Asymptomatic infections

As illustrated by multiple reports, significant proportion of SARS-CoV-2 infections is not associated with any symptom of the disease. For instance, Zhou (Clin Microb Inf 2020, see ***below***) monitored a cohort of 13 patients who were asymptomatic at the time of diagnosis. 12/13 presented with radiographic abnormalities from the time of diagnosis; 4/13 presented signs of radiographic progression; only 3/13 developed symptoms of the disease from 2 days after diagnosis. All patients became negative by PCR by day 18 at the latest.

Day (BMJ 2020, see ***below***) reported data from approx. 3000 individuals in an Italian village and showed that a majority of people infected with SARS-CoV-2 (50-75%) were asymptomatic. Similarly, Kimball (MMWR 2020, see ***below***) reported facility-wide testing in long-term care facility, which identified a 30.3% prevalence of infection among residents. Approximately half of the residents with positive test results did not have any symptoms at the time of testing.

In some cases, apparent asymptomatic infections may actually correspond to presymptomatic patients. In another example, Hu (Sci China Life Sci 2020, see ***below***) presented the clinical characteristics of 24 cases with asymptomatic infection screened from close contacts in Nanjing, China. None of the 24 asymptomatic cases reported any obvious symptoms when nucleic acid screening was performed. Five cases (20.8%) developed symptoms (fever, cough, fatigue, etc.) during hospitalization. Twelve (50.0%) cases showed typical CT images of ground-glass chest and 5 (20.8%) presented stripe shadowing in the lungs. The remaining 7 (29.2%) cases showed normal CT image and had no symptoms during hospitalization. These 7 cases were younger (median age: 14.0 years; P=0.012) than the rest.

A number of studies aimed at quantifying the proportion of asymptomatic infections. As indicated by Nishiura (Int J Inf Dis 2020, see ***below***), the asymptomatic ratio is conventionally estimated using sero-epidemiological data. However, such data were not available at the beginning of the epidemic. Instead, the authors estimated the asymptomatic ratio by using information on Japanese nationals that were evacuated from Wuhan, China on chartered flights. Based on this very small sample size, the asymptomatic ratio was estimated at 30.8% (95% confidence interval (CI): 7.7%, 53.8%) among evacuees. Mizumoto (Euro Surveill 2020, see ***below***) derived the delay-adjusted asymptomatic proportion of infections cases on board the Diamond Princess cruise ship. The estimated asymptomatic proportion reached a somewhat lower value of 17.9% (95% credible interval (CrI): 15.5-20.2%), overlapping the confidence interval of the estimate of Nishiura.

In a more recent publication, Han (Int J Biol Sci 2020, see ***below***) indicated that the proportion of asymptomatic individuals among all confirmed cases widely differed (from 1.95% to 87.9%) according to the study setting and the populations studied.

Re-infections

A key question for COVID-19 has long been whether true re-infection occurs (To, Hung et al. Clin Inf Dis 2020, see ***below***). Although neutralizing antibody develops rapidly after infection, antibody titers start to decline as early as 1-2 months after the acute infection. Due to prolonged viral shedding at low levels near the detection limit of RT-PCR assays, patients tested negative and discharged from hospitals are often having recurrence of positive results. A case report suggested that re-infection may occur, but viral genome analysis was not performed to confirm this conclusion. According to the media, additional re-infection cases have been found in Europe, but the observations not published in a scientific journal (https://www.euronews.com/2020/08/25/two-cases-of-covid-19-reinfection-reported-in-europe). These reported cases couldn't put an end to the controversy between persistent virus shedding and re-infection. However, on Aug 25th 2020, To, Hung et al. (Clin Inf Dis 2020, see ***below***) reported on a 33-year old male residing in Hong Kong with a second episode of infection which occurred 4.5 months after the first episode. Re-infection was confirmed using whole genome analysis to discriminate re-infection from prolonged viral shedding, and was also supported by epidemiological, clinical and serological data. The authors noted that this confirmation of re-infection has important implications. In particular, herd immunity appears less likely to eliminate SARS-CoV-2, although it is possible that subsequent infections may be milder than the first infection as observed for this patient. Of note, re-infection is common for "seasonal" coronaviruses 229E, OC43, NL63 and HKU1. In some instances, re-infection occurs despite a static level of specific antibodies. These data also have implications on vaccine development.

Another case of re-infection was reported two days later by Tillett (Lancet Inf Dis, see ***below***), who described the data from an investigation of two instances of SARS-CoV-2 infection in a same twenty-five year old individual in the US. Through nucleic acid sequence analysis, the viruses associated with each instance of infection were found to possess a degree of genetic discordance that cannot be explained reasonably through short-term *in vivo* evolution. Interestingly, in this case, symptoms consistent with COVID-19 were associated with both infections. The generalizability of this finding remains unknown.

A subsequent publication from the European CDC on September 21 2020 described a total of 6 cases of re-infection, including both symptomatic and asymptomatic infections (https://www.ecdc.europa.eu/en/publications-data/threat-assessment-brief-reinfection-sars-cov-2). An additional case of reinfection with a new strain harbouring the S variant D614G was reported by Goldman (manuscript on medRxiv, see ***below***).

Case fatality rate

Case fatality rate in China

Early data from China yielded an estimated mortality of the COVID-19 of approximately 2.84%, based on 1 975 infections and 56 deaths reported in 26 days following the first official announcement of the epidemic (Wang, Tang et al. J Med Virol 2020, see ***below***). Data available by October 20 2020 12:00 CET pointed towards a higher value (91 546 confirmed cases and 4746 deaths in China, corresponding to 5.18%) (WHO dashboard at https://covid19.who.int/). At global level (40 114 293 confirmed cases and 1 114 692 deaths) the same day, the estimate reached 2.78%.

Obviously, this type of estimate has to be taken with a lot of caution. As indicated by Kobayashi (J Clin Med 2020, see ***below***), the observed dataset of reported cases represents only a proportion of all infected individuals and there can be a substantial number of asymptomatic and mildly infected individuals who are never diagnosed. Several authors suggested that the number of reported cases of the disease, in China as well as in other countries, is likely to be underestimated (see for instance De Salazar on medRxiv:

https://www.medrxiv.org/content/10.1101/2020.02.13.20022707v1). Battegay (Swiss Med Wkly 2020, see ***below***), like Kobayashi (J Clin Med 2020, see ***below***) or Baud (Lancet Inf Dis 2020, see ***below***), also pointed to the fact that diagnosis of COVID-19 infection will precede recovery or death by days to weeks and that the number of deaths should therefore be compared to the past case counts. Lack of a standardized case definition also affects estimates of case fatality rates (see ***Case definition*** below).

Other authors, like Spychalski (Lancet Infect Dis 2020, see ***below***) showed that the case fatality rate calculated per total cases seems to remain the best tool to express the fatality of the disease, even though it might underestimate this figure in the initial phase of an outbreak.

Ji, Ma et al. (Lancet 2020, see ***below***) highlighted the difference in mortality rates between Hubei and other Chinese provinces. The authors postulated that this difference is likely to be related to the rapid escalation in the number of infections around the epicentre of the outbreak, which has resulted in an insufficiency of health-care resources, thereby negatively affecting patient outcomes in Hubei, while this has not yet been the situation for the other parts of China.

A similar observation was made by Mizumoto (Em Inf Dis 2020, see ***below***), who estimated the time-delay adjusted risk for death from COVID-19 as of February 28, 2020 in China. The estimates of the risk for death in Wuhan reached values as high as 12% in the epicenter of the epidemic and ≈1% in other, more mildly affected areas. Comparable results were obtained by Wilson (Em Inf Dis 2020, see ***below***), who reported case-fatality risks, when adjusted for a 13-day lag time from reporting to death, of 3.5% in China and 0.8% in China, excluding Hubei Province.

Nevertheless, according to the large retrospective study reported by the Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (Zhonghua Liu Xing Bing Xue Za Zhi 2020, see ***below***; and Wu JAMA 2020, see ***below***), based on the 72 314 reports received through February 11 2020 by the Chinese Centre for Disease Control and Prevention in mainland China, 1023 deaths were observed out of a total of 44 672 confirmed cases, corresponding to a case-fatality rate of 2.3%. This analysis also showed that the case-fatality rate is largely influenced by the age of the patients (***Table 5***).

Of note, the WHO-China Joint Mission on Coronavirus Disease 2019 Mortality, which presented data on 2114 COVID-19 related deaths among 55 924 laboratory-confirmed cases in China, also reported the highest mortality among people over 80 years of age, with a case fatality rate of 21.9% (https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf).

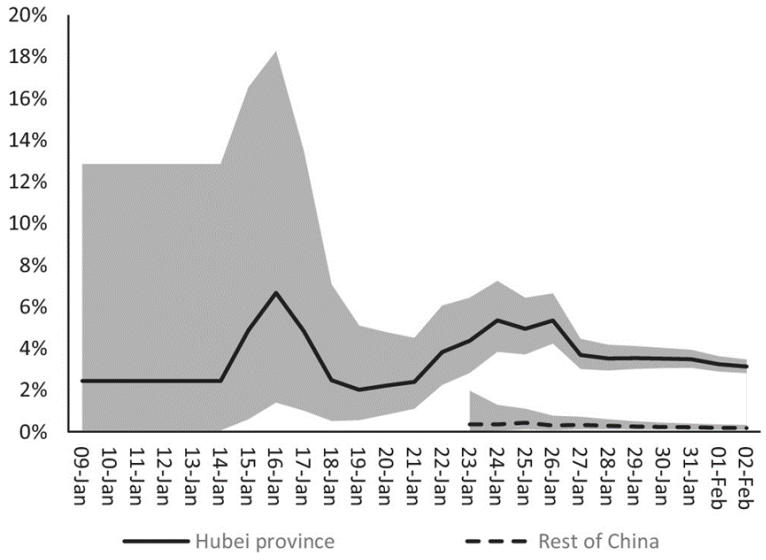
Table 5 Patients, deaths, and case fatality rates, as well as observed time and mortality for n=44,672 confirmed COVID-19 cases in Mainland China as of February 11, 2020 (from The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team Zhonghua Liu Xing Bing Xue Za Zhi 2020).

Baseline Characteristics	Confirmed Cases, N (%)	Deaths, N (%)	Case Fatality Rate, %
Overall	44,672	1,023	2.3
Age, years			
0–9	416 (0.9)	–	–
10–19	549 (1.2)	1 (0.1)	0.2
20–29	3,619 (8.1)	7 (0.7)	0.2
30–39	7,600 (17.0)	18 (1.8)	0.2
40–49	8,571 (19.2)	38 (3.7)	0.4
50–59	10,008 (22.4)	130 (12.7)	1.3
60–69	8,583 (19.2)	309 (30.2)	3.6
70–79	3,918 (8.8)	312 (30.5)	8.0
≥80	1,408 (3.2)	208 (20.3)	14.8

A study by Wu (Nat Med 2020: https://www.nature.com/articles/s41591-020-0822-7) provided somewhat lower estimates of the case fatality rate in Wuhan, of 0.3% (0.1–0.7%), 0.5% (0.3–0.8%) and 2.6% (1.7–3.9%) for those aged <30 years, 30–59 years and >59 years, respectively.

Using a different approach, and based on early data, Wu (Eurosurv 2020, see ***below***) also estimated the risk of fatality among hospitalised cases at 14% (95% confidence interval: 3.9-32%). This estimate of the hospital fatality risk remained fairly stable over the 10-day period since the first death was announced on 11 January. Subsequently, Leung (Rev Med Vir 2020, see ***below***) calculated that as of 2 February 2020, over 17 000 cases were confirmed in China, with a hospital fatality rate of 2.1%; in Hubei province, the hospital fatality rate reached 3.1%, significantly above the rest of China (***Figure 10***).

Figure 10 Trends of hospital fatality rates in Hubei province and the rest of China with 95% CI (from Leung Rev Med Vir 2020)



Case fatality rate outside China

Based on data up to Feb 8th, Verity found estimates of case fatality ratio from international cases stratified by age to be consistent with those from China (Lancet Inf Dis 2020, see ***below***).

Wilson (on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.15.20023499v1) considered symptomatic cases outside of China (countries/settings with 20+ cases) and the proportion who are in intensive care units (4.0%, 14/349 on 13 February 2020). Given what is known about case fatality rates for intensive care unit patients with severe respiratory conditions from a meta-analysis, he estimated a case fatality rate of 1.37% (95%CI: 0.57% to 3.22%) for COVID-19 cases outside of China. Using data as of as of March 5 2020, Wilson (Em Inf Dis 2020, see ***below***) also reported a case fatality estimate in 82 countries, territories, and areas reaching 4.2%.

Rajgor (Lancet Inf Dis 2020, see ***below***) acknowledged the level of variability of COVID-19 case fatality rate estimates, and noted that a unique situation has arisen for estimating the case fatality rate with the outbreak onboard the Diamond Princess cruise ship. This scenario provided a population living in a defined territory without most other confounders, such as imported cases, defaulters of screening, or lack of testing capability. 3711 passengers and crew were onboard, of whom 705 became sick and tested positive for COVID-19 and seven died, giving a case fatality rate of 0.99%. If the passengers onboard were generally of an older age, the case fatality rate in a healthy, younger population could be lower.

The systematic review of COVID-19 epidemiology by Park (J Clin Med 2020, see ***below***), which included 41 studies, indicated that current model-based estimates ranged from 0.3% to 1.4% for outside China.

In June, another systematic review and meta-analysis by Grant (PLoS One 2020, see ***below***) found a hospital fatality rate of 7% (73 studies, 10 402 patients).

Italy

Based on the first 888 cases confirmed in Italy, Porcheddu (J Infect Dev Ctries 2020, see ***below***) noted that the case fatality rate in China and Italy were identical at 2.3%. Livingston (JAMA 2020, see ***below***) provided a case fatality rate per age group in Italy. It was found to increase with age, up to 22.7% in subjects 90 years of age and older. A subsequent report by Onder (JAMA 2020, see ***below***) mentioned an overall fatality rate of persons with confirmed COVID-19 of 7.2% (calculated as number of deaths/number of cases), and a case fatality rate of 20.2% in subjects >80 years of age in Italy. Deaths were said to be mainly observed among older, male patients with multiple comorbidities. However, the data presented by Onder remained limited, and derived from the first month of documented COVID-19 cases in Italy.

Barone-Adesi (Disaster Med Public Health Prep 2020, see ***below***) commented on the higher case-fatality rate observed in Italy compared to China, and suggested that the Italian testing strategy could explain an important part of the observed difference. The majority of patients that are currently tested in Italy have severe clinical symptoms that usually require hospitalization. Indeed, the proportion of positive cases that are admitted to the hospital in Italy is about 40% (and used to be much higher in previous weeks), while it was about 10-20% in China. As the positive cases resulting from this testing strategy are so skewed towards more serious conditions, it is not surprising that a higher case fatality rate is observed.

Another study rejected the possibility that social habits and intergenerational contacts contribute to explain the number of deaths observed in Italy (Giangreco J Trav Med 2020, see ***below***)

U.S.A.

Preliminary reports from 4226 patients with COVID-19 in the United States indicated that fatality was highest in persons aged ≥85, ranging from 10% to 27%, followed by 3% to 11% among persons aged 65–84 years, 1% to 3% among persons aged 55-64 years, <1% among persons aged 20–54 years, and no fatalities among persons aged ≤19 years (CDC COVID-19 Response Team MMWR Morb Mortal Wkly Rep 2020, see ***below***).

McMichael (NEJM 2020, see ***below***) described an outbreak linked to a long-term care facility in the U.S. (Washington state). Case-fatality rate among residents (median age 83 years, ranging from 51 to 100) reached 35%.

India

As of July 3, 2020, India reported a fatality rate of 2.8%, among the lowest in the world (Samaddar Front Genet 2020, see ***below***). Also, the severity of the disease was found much less among Indians as evidenced by the low rate of ICU admission (15.3%) and the need for mechanical ventilation (4.16%). Samaddar hypothesized that several factors might have some role in reducing the susceptibility of Indians to COVID-19. Data available by October 20 2020 12:00 CET still point towards a relatively low value (7 597 063 cases and 115 197 deaths in India, corresponding to 1.52% (WHO dashboard at https://covid19.who.int/). Most recent data from the Indian states of Tamil Nadu and Andhra Pradesh provided more detailed estimates of mortality in India (Laxminarayan Science 2020, see ***below***). Case fatality ratios spanned 0.05% at ages of 5 to 17 years to 16.6% at ages of 85 years or more.

Special populations

Elderly

In the study reported by Chen (Lancet 2020, see ***below***), COVID-19 was found more likely to affect older males with comorbidities. The impact of age as well as gender and comorbidities is described in the section ***Risk factors*** below.

Haemodialysis patients

A manuscript by Ma depicted 42 cases of disease in a cohort of 230 haemodialysis patients in Wuhan (https://www.medrxiv.org/content/10.1101/2020.02.24.20027201v3). Despite the death of 10 patients with COVID-19 vs. 3 without COVID-19 during the study, the symptoms reported for most of the patients were mild, and there were only 3 cases admitted to ICU.

Cancer patients

Data are available to show that cancer patients seem to be at increased risk of COVID-19 and increased risk of severe events (see section *Error! Reference source not found.* below).

Immunocompromised patients

Minotti (J Inf 2020, see ***below***) identified 16 publications with 110 immunosuppressed patients, mostly presenting cancer, along with transplantation and immunodeficiency. Cancer was more often associated with a more severe course, but not necessarily with a bad prognosis. The data showed that both children and adults with immunosuppression seemed to have a favourable disease course, as compared to the general population. The authors indicated that this observation might be explained by a hypothetical protective role of a weaker immune response, determining a milder disease presentation and thus underdiagnosis.

More recently, a review by Cajamarca-Baron (Reumatol Clin 2020, see ***below***) confirmed that patients with cancer and recent cancer treatment (chemotherapy or surgery) and SARS-CoV-2 infection have a higher risk of worse outcomes. In transplant patients (renal, cardiac and hepatic), with neurological pathologies (multiple sclerosis, neuromyelitis optica [NMODS], myasthenia gravis [MG]), primary immunodeficiencies and infection with human immunodeficiency virus (HIV) in association with immunosuppressants, studies have shown no tendency for worse outcomes.

Primary Antibody Deficiencies patients

Quinti (J Allergy Clin Immunol 2020, see ***below***) identified seven Primary Antibody Deficiencies (PAD) patients with COVID-19 infection: five affected with Common Variable Immune Deficiencies (CVIDs) and two affected with Agammaglobulinemia, one with X-linked Agammaglobulinemia (XLA) and one with Autosomal Recessive Agammaglobulinemia (ARA). All PAD patients have defective antibody production. Patients with Agammaglobulinemia lack B lymphocytes whereas patients with Common Variable Immune Deficiency have dysfunctional B lymphocytes. In

patients affected with agammaglobulinemias, the COVID-19 course was characterized by mild symptoms, short duration, with no need of treatment with the immune-modulating drug blocking IL-6, and had a favourable outcome. In contrast, patients affected with Common Variable Immune Deficiencies presented with a severe form of the disease requiring multiple drug treatment, including antiretrovirals agents and IL-6 blocking drugs, and mechanical ventilation. The strikingly different clinical course of COVID-19 in patients with agammaglobulinemia compared to CVIDs cannot be explained by the level of serum immunoglobulins which were similarly low in all PAD patients at diagnosis.

Children

Paediatric data from China

The first confirmed paediatric case of SARS-CoV-2 infection is said to have been reported in Shenzhen on January 20 (Cao J Formos Med Assoc 2020, see ***below***). By January 30, there were 28 children (1 month to 17 years) with confirmed infection in China (Shen World J Pediatr 2020, see ***below***). The clinical features appeared variable. Several patients displayed no obvious clinical symptoms at diagnosis, and they were found by screening because of close contacts with confirmed patients; and further chest imaging suggested pneumonia. Several gradually presented with fever, fatigue, dry cough, accompanied by other upper respiratory symptoms including nasal congestion, runny nose, and seldom gastrointestinal symptoms such as nausea, vomiting and diarrhoea. Laboratory examination in paediatric patients showed that blood routine was often normal, and C-reactive protein was normal or transiently elevated. Lung imaging examination revealed mild increase of lung markings or ground-glass opacity or pneumonia. Most paediatric patients had mild symptoms, without fever or pneumonia. They had good prognosis and recovered within 1-2 weeks after disease onset. Only a few patients had lower respiratory tract infections. No severe cases or deaths have been reported in the paediatric population up to now.

With the progression of the outbreak, the first infant case was reported from Xiaogan, Hubei province. This was a 3-month-old female infant who had fever for one day and as discharged uneventfully 2 weeks later (Cao J Formos Med Assoc 2020, see ***below***). A subsequent retrospective study described 9 cases in children (7 females/2 males) aged 1 to 11 months (Wei JAMA 2020, see ***below***). Four patients were reported to have fever, 2 had mild upper respiratory tract symptoms, 1 had no symptoms but tested positive for COVID-19 in a designated screening because of exposure to infected family members, and 2 had no information on symptoms available. None of the 9 infants required intensive care or mechanical ventilation or had any severe complications.

Liu (NEJM 2020, see ***below***) retrospectively reported 6 paediatric cases treated in Wuhan hospitals in January 2020. One of the 6 children was admitted to the paediatric intensive care unit. All the patients recovered after hospitalization for a median of 7.5 days (range, 5 to 13).

Xia (Pedriatr Pulmonol 2020, see ***below***) presented the clinical, laboratory, and chest CT features of 20 paediatric inpatients with COVID-19 in Wuhan. Fever (12/20, 60%) and cough (13/20, 65%) were the most common symptoms. Procalcitonin elevation was found frequently (16/20, 80%).

A case in a 55 day-old infant was reported in detail by Cui (J Infect Dis 2020, see ***below***). The patient initially presented with mild dry cough and no fevers. However, symptoms became gradually worse from day 7 to day 11 of illness, and symptomatic support was strengthened. This case highlighted that infants with COVID-19 can also present with multiple organ damage and rapid disease changes.

The retrospective Chinese study involving COVID-19 cases reported through February 11, 2020, and corresponding to 44672 confirmed cases, 549 cases were identified in the 10-19 years age group (1%) and 416 cases among children less than 10 years (1%) (Wu JAMA 2020, see ***below***).

Lu (NEJM 2020, see ***below***) tested 1391 children from January 28 through February 26, 2020 in Wuhan, of whom a total of 171 (12.3%) were confirmed to have SARS-CoV-2 infection. The median age of the infected children was 6.7 years. Fever was detected in 41.5%. Other common signs and symptoms included cough and pharyngeal erythema. A total of 27 patients (15.8%) did not have any symptoms of infection or radiologic features of pneumonia. A total of 12 patients had radiologic features of pneumonia but did not have any symptoms of infection. During the course of hospitalization, 3 patients required intensive care support and invasive mechanical ventilation; all had coexisting conditions (hydronephrosis, leukemia, and intussusception). Lymphopenia was present in 6 patients (3.5%). The most common radiologic finding was bilateral ground-glass opacity (32.7%). As of March 8, 2020, there was one death: a 10-month-old child with intussusception had multiorgan failure and died 4 weeks after admission.

Another large paediatric cohort in China was reported by Dong (Pediatrics 2020, see ***below***). There were 731 (34.1%) laboratory-confirmed cases and 1412 (65.9%) suspected cases. The median age of all patients was 7 years (interquartile range: 2-13). Over 90% of all patients were asymptomatic, mild, or moderate cases.

From a systematic review of COVID-19 in children, Ludvigsson (Acta Paediatr 2020, see ***below***) identified 45 relevant scientific papers and letters describing mostly paediatric cases from China. The data showed that children have so far accounted for 1-5% of diagnosed COVID-19 cases, that they often have milder disease than adults and deaths have been extremely rare. Diagnostic findings have been similar to adults, with fever and respiratory symptoms being prevalent, but fewer children seem to have developed severe pneumonia. Elevated inflammatory markers were less common in children and lymphocytopenia seemed rare.

Paediatric data from other countries

In an early report, Wong (JAMA 2020, see ***below***) mentioned 3 confirmed paediatric cases in Singapore. The patients were very young (6 months, 1 year and 2 years) and had very mild symptoms.

Park (J Korean Med Sci 2020, see ***below***) reported the first paediatric case of COVID-19 in Korea, a 10-year-old girl who presented mild clinical course of her pneumonia that did not require antiviral treatment.

Shekerdemian (JAMA Ped 2020, see ***below***) presented the outcome of a cross-sectional study that included children positive for COVID-19 admitted to 46 North American PICUs between March 14 and April 3, 2020 with follow-up to April 10, 2020. Of the 48 children with COVID-19 admitted, 25 (52%) were male, and the median (range) age was 13 (4.2-16.6) years. Forty patients (83%) had significant preexisting comorbidities; 35 (73%) presented with respiratory symptoms and 18 (38%) required invasive ventilation. Eleven patients (23%) had failure of 2 or more organ systems. Extracorporeal membrane oxygenation was required for 1 patient (2%). Targeted therapies were used in 28 patients (61%), with hydroxychloroquine being the most commonly used agent either alone (11 patients) or in combination (10 patients). At the completion of the follow-up period, 2 patients (4%) had died and 15 (31%) were still hospitalized, with 3 still requiring ventilatory support and 1 receiving extracorporeal membrane oxygenation.

Mahase (BMJ April 28 2020, see ***below***) described a rising number of children presenting with a multisystem inflammatory state in the UK. The cases had in common "overlapping features of toxic shock syndrome and atypical **Kawasaki disease** with blood parameters consistent with severe COVID-19 in children. Kawasaki disease is a rare vasculitis of childhood that can cause coronary-artery aneurysms. Similar reports circulated in French media (see for instance https://www.connexionfrance.com/French-news/France-warns-of-child-illness-similar-to-Kawasaki-disease-that-may-be-Covid-19-linked). A cluster of eight children with hyperinflammatory shock, showing features similar to atypical Kawasaki disease, Kawasaki disease shock syndrome, or toxic shock syndrome (typical number is one or two children per week) has been described by Riphagen (Lancet 2020, see ***below***). All children were previously fit and well. Six of the children were of Afro-Caribbean descent, and five of the children were boys. All children except one were well above the 75th centile for weight. All children progressed to warm, vasoplegic shock, refractory to volume

resuscitation and eventually requiring noradrenaline and milrinone for haemodynamic support. Most of the children had no significant respiratory involvement, although seven of the children required mechanical ventilation for cardiovascular stabilisation. Other notable features (besides persistent fever and rash) included development of small pleural, pericardial, and ascitic effusions, suggestive of a diffuse inflammatory process. One child developed arrhythmia with refractory shock, requiring extracorporeal life support, and died from a large cerebrovascular infarct.

On May 15, a WHO publication mentioned the need to characterize this syndrome and its risk factors, to understand causality, and describe treatment interventions. To that end, a preliminary case definition and case report form for **multisystem inflammatory disorder** in children and adolescents was issued (https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19).

Feldstein (NEJM 2020, see) conducted targeted surveillance for multisystem inflammatory syndrome - from March 15 to May 20, 2020, in paediatric health centres across the United States, and reported on 186 patients. The median age was 8.3 years, 115 patients (62%) were male, 135 (73%) had previously been healthy, 131 (70%) were positive for SARS-CoV-2 by RT-PCR or antibody testing, and 164 (88%) were hospitalized after April 16, 2020. Organ-system involvement included the gastrointestinal system in 171 patients (92%), cardiovascular in 149 (80%), hematologic in 142 (76%), mucocutaneous in 137 (74%), and respiratory in 131 (70%). The median duration of hospitalization was 7 days (interquartile range, 4 to 10); 148 patients (80%) received intensive care, 37 (20%) received mechanical ventilation, 90 (48%) received vasoactive support, and 4 (2%) died. Coronary-artery aneurysms (z scores ≥2.5) were documented in 15 patients (8%), and Kawasaki's disease-like features were documented in 74 (40%). Most patients (171 [92%]) had elevations in at least four biomarkers indicating inflammation. The use of immunomodulating therapies was common: intravenous immune globulin was used in 144 (77%), glucocorticoids in 91 (49%), and interleukin-6 or 1RA inhibitors in 38 (20%). Multisystem inflammatory syndrome in children associated with SARS-CoV-2 therefore appeared as serious and life-threatening illness.

Andina (Pediatr Dermatol. 2020, see ***below***) presented a series of 22 cases of **chilblains** in children and adolescents in the setting of COVID-19 seen in a very short period of time in the Emergency Department of a children's hospital in Madrid. Chilblains, aka pernio, perniosis, or kibes, is a localized inflammatory skin disorder characterized by erythrocyanotic skin lesions induced by non-freezing cold exposure. Chilblains associated with COVID-19 became increasingly described in the medical literature. More details on this cutaneous manifestation can be found in the narrative review by Ladha (J Cut Med Surg 2020, see ***below***).

Systematic reviews and meta-analyses

A systematic review by Castagnoli (JAMA Pediatr 2020, see ***below***) identified seventeen studies conducted in China and one in Singapore, including a total of 1065 paediatric cases of SARS-CoV-2 infection. Data from this review showed that most children and adolescents who were infected by SARS-CoV-2 (i.e., tested positive by nasopharyngeal swab) presented with mild symptoms. Frequent clinical manifestations included fever, dry cough, and fatigue accompanied by other upper respiratory symptoms, such as nasal congestion and runny nose. Moreover, the main gastrointestinal symptoms were nausea, vomiting, and diarrhoea, which were reported in a few cases, particularly in a newborn and infants. In this analysis, only one paediatric case presented with severe lower respiratory tract infection (COVID-19 pneumonia), complicated by shock and kidney failure, and fortunately, it was successfully treated with intensive care.

The review by Hasan (Cureus 2020, see ***below***) provided a summary of laboratory and clinical imaging data in children.

A systematic review by Meena (Indian Ped 2020, see ***below***) included 27 studies (4857 patients). It found that about half of the patients had each of fever and cough, 11% (6-17%) had fast breathing, and 6-13% had gastrointestinal manifestations. Most of the patients had mild to moderate disease, and only 4% had a severe or critical illness. Leukopenia was the commonest reported laboratory abnormality.

A more recent publication by Kharoud (on medRxiv, see ***below***), including 37 studies (668 children in total) conducted between January 1, 2020, and July 15, 2020, provided other estimates of the pooled prevalence of various symptoms and laboratory findings of COVID-19 in the paediatric population. The most prevalent symptom of COVID-19 in children was 46.17% (95%CI 39.18-53.33%), followed by cough (40.15%, 95%CI 34.56-46.02%). Less common symptoms were found to be dyspnoea, vomiting, nasal congestion/rhinorrhoea, diarrhoea, sore throat/pharyngeal congestion, headache, and fatigue. The prevalence of asymptomatic children was 17.19% (95%CI 11.02-25.82%). The most prevalent laboratory findings in COVID-19 children were elevated Creatinine Kinase (26.86%, 95%CI 16.15-41.19%) and neutropenia (25.76%, 95%CI 13.96-42.58%). These were followed by elevated LDH, thrombocytosis, lymphocytosis, neutrophilia, elevated D Dimer, Elevated CRP, elevated ESR, leucocytosis, elevated AST and leukopenia. There was a low prevalence of elevated ALT and lymphopenia in children with COVID- 19.

A retrospective analysis by Wang (Sci Rep 2020, see ***below***) focused on gastrointestinal symptoms and faecal nucleic acid detection in paediatric COVID-19 patients from January 1, 2020 to August 10, 2020. The authors found that the most common gastrointestinal symptoms in children with COVID-19 were vomiting and diarrhoea, with a total incidence of 17.7% (95% Cl 13.9-21.5%). However, the prevalence of gastrointestinal symptoms in other countries (21.1%, 95% CI 16.5-25.7%) was higher compared to China (12.9%, 95% CI 8-17.7%). In Wuhan, the pooled prevalence was much higher (41.3%, 95% CI 3.2-79.4%) compared to areas outside Wuhan in China (7.1%, 95% CI 4.0-10.3%).

Kaushik (Pediatr Infect Dis J 2020, see ***below***) provided a systematic review of the multisystem inflammatory syndrome associated with SARS-CoV-2 infection in children. A total of 328 articles published from January 1, 2020, to July 31, 2020 were identified. Sixteen studies with 655 participants (3 months-20 years of age) were included in the final analysis. Most of the children in reported studies presented with fever, gastrointestinal symptoms, and Kawasaki Disease-like symptoms. Sixty-eight percent of the patients required critical care; 40% needed inotropes; 34% received anticoagulation; and 15% required mechanical ventilation. More than two-thirds of the patients received intravenous immunoglobulin and 49% received corticosteroids. Remdesivir and convalescent plasma were the least commonly utilized therapies. Left ventricular dysfunction was reported in 32% of patients. Among patients presenting with Kawasaki Disease-like symptoms, 23% developed coronary abnormalities and 26% had circulatory shock. The majority recovered; 11 (1.7%) children died.

Risk of infection in children

While the disease seems to have a milder course in children than adults, a manuscript by Qifang Bi on medRxiv (https://www.medrxiv.org/content/10.1101/2020.03.03.20028423v1) suggested that children are at a similar risk of infection as the general population. This conclusion was driven from 391 cases and 1286 close contacts identified by the Shenzhen CDC. However, other lines of evidence pointed to a different attack rate of the disease in children compared to adults. In Iceland, Gudbjartsson (NEJM 2020, see ***below***), carried out both targeted testing of persons at high risk for infection and population screening by RT-PCR. Children under 10 years of age were less likely to be found positive than were persons 10 years of age or older (6.7% vs. 13.7% for targeted testing; 0% vs. 0.8% in the population screening). In China, a household cohort study found a secondary attack rate in children of 4% comparing with 17.1% in adults (Li, Zhang et al. Clin Inf Dis 2020, see ***below***).

Pregnancy and newborns

In general, pregnancy is a physiological state in which women are more susceptible to respiratory pathogens and severe pneumonia, due to an immunosuppressive state and various physiological adaptive changes (e.g., diaphragm elevation, increased oxygen consumption, and oedema of respiratory tract mucosa). It is therefore reasonable to predict that pregnant women might be at greater risk for severe illness. Previous epidemics of other CoVs have typically resulted in severe complications during pregnancy such as maternal morbidity and mortality, perinatal infections and death (Wong Am J Obstet Gynecol 2004, see ***below***; Alfaraj J Microbiol Immunol Infect 2019, see ***below***). However, unlike CoV infections of pregnant women caused by SARS and MERS, pregnant women are not more

susceptible to COVID-19, nor are they at risk of more severe disease than the non-pregnant population. There is no clear evidence of vertical transmission of COVID-19 from the mother to the foetus. Several recent publications reviewed available information on COVID-19 in pregnant women (see for instance Diriba Eur J Med Res 2020, see ***below***; Yee Sci Rep 2020, see ***below***).

Clinical characteristics of pregnant woman with COVID-19 infection

Multiple studies have observed the clinical characteristics of COVID-19 pneumonia in pregnant women. Most early data stemmed from case reports and small case series[3], but a higher level of evidence soon became available (Li Clin Inf Dis 2020, see ***below***; Zaigham Acta Obstet Gynecol Scand 2020, see ***below***; Qiancheng Int J Infect Dis 2020, see ***below***; Yang J Matern Fetal Neonatal Med 2020, see ***below***). The clinical characteristics of COVID-19 pneumonia in pregnant women seem to be similar to those reported for non-pregnant adults with COVID-19 pneumonia. Briefly, the most commonly reported symptoms are fever and cough, followed by fatigue, diarrhoea, dyspnoea, sore throat, and myalgia (Yang J Matern Fetal Neonatal Med 2020, see ***below***).

Reports on asymptomatic COVID-19 infected pregnant women have been made available, following the implementation of screening practices. In March 2020, Chen, Liao et al. (J Med Virol 2020, see ***below***) reported that SARS-CoV-2 infection could asymptomatically occur during gestation, but was diagnosed after delivery. Another study by Sutton (NEJM 2020, see ***below***) described 33 pregnant women who tested positive for COVID-19, of whom 29 (87,9%) showed no symptoms of the disease. The authors recommended universal testing for all pregnant women admitted to the labour unit.

A few pregnant women afflicted with severe respiratory morbidity have been reported in relation to COVID-19 (for instance, Hong Case Rep Womens Health 2020, see ***below***). Two studies reported a total of three cases of maternal ICU admission (Breslin, Baptiste , Miller et al. Am J Obst & Gynecol MFM 2020, see ***below***; Alzamora Am J Perinatol 2020; see ***below***). All mothers had obesity class II or more and type 2 diabetes mellitus. A recent multicenter study reported nine pregnant women with severe COVID-19 infection (Hantoushzadeh Am J Obstet Gynecol 2020, see ***below***). At the time of reporting 7 of 9 died, 1 of 9 remained critically ill and ventilator-dependent, and 1 of 9 recovered after prolonged hospitalization. Complications of COVID-19, such as cardiomyopathy and thromboembolism, have also been seen in the pregnant population (for instance, Juusela Am J Obst Gynecol MFM 2020, see ***below***; Martinelli Thromb Res 2020, see ***below***).

Perinatal complications

Pregnancy may not increase susceptibility to COVID-19 infection or influence the severity of the disease, but SARS-CoV-2 infection does seem to influence pregnancy. Severe pneumonia during pregnancy (regardless of the causative agent) increases the risk of preterm delivery, foetal growth restriction, low birth weight and low Apgar score at birth.

Regarding perinatal outcomes, most authors did not report adverse events (Chen Guo Lancet 2020, see ***below***; Zhang Zhonghua Fu Chan Ke Za Zhi 2020, see ***below***; Wang Clin Inf Dis 2020, see ***below***; Yu Lancet Inf Dis 2020, see ***below***; Liu AJR Am J Roentgenol 2020, see ***below***; Yan Am J Obstet Gynecol 2020, see ***below***). However, a meta-analysis on pregnancy outcome in COVID-19 patients found preterm birth to be the most common adverse pregnancy outcome (Di Mascio Am J Obst & Gynecol MFM 2020, see ***below***). Li (Clin Inf Dis 2020, see ***below***) found a higher incidence rate of premature delivery in confirmed cases (18,8%) compared to two control groups (5%), but none was due to severe maternal respiratory failure.

[3] See for instance Chen Guo Lancet 2020; Liu, Chen J Inf 2020; Chen Huang Zhonghua Bing Li Xue Za Zhi 2020; Fan Clin Inf Dis 2020; Yu Lancet Inf Dis 2020

Zhu (Transl Ped 2020, see ***below***) presented the clinical features and outcomes of ten neonates, born to mothers with confirmed SARS-CoV-2 infection. One newborn died from multiple organ failure and disseminated intravascular coagulation (DIC).

A recent meta-analysis by Yee (Sci Rep 2020, see ***below***) including 11 studies involving 9032 pregnant women with COVID-19 and 338 infants, found around 30% preterm delivery. Foetal death and detection of SARS-CoV-2 were observed in about 2%, whereas neonatal death was found to be 0.4%.

Perinatal COVID-19 infection may have adverse effects on both neonate and mother. Though less serious than SARS-CoV, in which adverse outcomes were reported in 10 out of 12 pregnancies, COVID-19 pregnancy seems not to be without risk. COVID-19 has been shown to be associated with a cytokine-storm (Huang Lancet 2020, see ***below***). Abnormally elevated levels of TNF-α in maternal peripheral blood can be toxic to early embryo development and have been shown to induce preterm labour in non-human primate models (Yockey Immunity 2018, see ***below***). Furthermore, maternal inflammation as a result of viral infection during pregnancy can affect several aspects of foetal brain development and may lead to a wide range of neuronal and behavioural dysfunctions in postnatal life (Mor Nat Rev Immunol 2017, see ***below***).

Vertical transmission

In the first months of the epidemic, there was no evidence of vertical transmission of COVID-19. Repetitive negative samples of amniotic fluid, cord blood, neonatal throat swabs, placental tissue, genital fluid and breastmilk samples from COVID-19 infected mothers were reported in multiple studies (Chen Guo Lancet 2020, see ***below***; Chen Huang Zhonghua Bing Li Xue Za Zhi 2020, see ***below***; Yu Lancet Inf Dis 2020, see ***below***; Wang Guo Clin Inf Dis 2020, see ***below***; Zhu Transl Ped 2020, see ***below***; Yang Ultrasound Obstet Gynecol 2020, see ***below***; Khan Inf Contr Hosp Epi 2020, see ***below***; Liu Front Med 2020, see ***below***). However, more recent studies are now implying that vertical transmission may occur, although the proportion of pregnancies affected and the significance to the neonate has yet to be determined.

A cohort study by Zeng (JAMA Pediatr 2020, see ***below***) described 33 neonates born to mothers infected with COVID-19. Of these 33 neonates, 3 (9%) showed positive nasopharyngeal swabs on day 2 of life. Strict infection control and prevention measures were implemented during the delivery. Zhang (Eur Respir J 2020, see ***below***) described three cases of COVID-19 positive neonates delivered through caesarean section and under level III protection. No mother-child contact or breastfeeding had occurred and all newborn babies were at isolation when symptoms occurred. Alzamora (Am J Perinatol 2020; see ***below***) reported a case of a newborn who tested positive on RT-PCR of nasopharyngeal swab as soon as 16 hours after delivery. As in the cases mentioned above, there was a low probability of infection during the caesarean section or postnatally, due to sterility of the procedure and isolation measures implemented immediately after birth. Taken together, these findings strongly raised the suspicion of *in utero* transmission of SARS-CoV-2.

Furthermore, two articles from separate research teams in China presented 3 cases of neonates who may have been infected with COVID-19 *in utero* (Zeng JAMA 2020, see ***below***; Dong JAMA 2020, see ***below***). In these three newborns, elevated IgM and IgG antibodies were found following birth, while nasopharyngeal swabs tested negative on RT-PCR. IgG is passively transferred across the placenta from mother to foetus. IgM is too large to cross the placenta; thus, IgM must have been produced by the infant when the virus crossed the placenta. However, IgM assays can be prone to false-positive and false-negative results, along with cross-reactivity and testing challenges (Wang J Clin Microb 2020, see ***below***). Additionally, antibody levels decreased dramatically in the following weeks. Alzamora (Am J Perinatol 2020; see ***below***) also evaluated neonatal immunoglobulins in a SARS-CoV-2 positive neonate. The authors reported negative serology in both mother and neonate on the day of birth, with seroconversion of the mother on day 5. In contrast, neonatal serology remained negative. This could be explained by the immaturity of the adaptive immunity in the

neonatal period. The challenges with false-positive IgM test results, along with a rapid decline in IgM concentration and the fact that an immature immune system in the neonatal period may not be capable of developing IgMs, raises the possibility that the laboratory findings in the 3 infants in the first case reports are not evidence of true congenital infection but rather could represent artifact.

Zheng (Reprod Dev Med 2020: http://www.repdevmed.org/preprintarticle.asp?id=278679) described a very low expression of ACE2 in almost all human cell types of the early maternal-foetal interface, suggesting the placenta had virtually no susceptible cells to the virus. In contrast, Li, Chen et al. (PLoS One 2020, see ***below***) evaluated cell specific expression of ACE2 at the maternal-foetal interface as well as in multiple foetal organs. The authors found a high expression of ACE2 in maternal-foetal cells (stromal cells, perivascular cells of decidua, cytotropho- and syncitiotrophoblast in placenta). ACE2 expression was also found in specific cell types of human foetal heart, liver and lung, but not in kidney. They concluded that both the vertical transmission and the placenta dysfunction/abortion caused by SARS-CoV-2 need to be further carefully investigated in clinical practice.

All studies above described pregnancies in their third trimester, therefore the time interval from clinical manifestation of SARS-CoV-2 infection to delivery was short. The placental barrier is capable of delaying the transfer of the virus from mother to foetus; therefore, it remains uncertain whether there could be a risk of vertical transmission when SARS-CoV-2 infection occurs earlier in the pregnancy. A study on SARS-CoV-2 infected pregnant women in early pregnancy was reported by Yu (Lancet Inf Dis 2020, see ***below***). Two pregnant women were diagnosed with COVID-19 in the first trimester of pregnancy. In the second trimester, both patients tested positive for SARS-CoV-2 total antibodies in serum, while nasopharyngeal swabs were negative. The results of RT-PCR tests of the patients' amniotic fluid were negative, and tests for SARS-CoV-2 IgM and IgG in amniotic fluid were also negative. However, RNA is much less stable in amniotic fluid than is DNA and the virus might have been undetectable in amniotic fluid because of insufficient gestational age. Therefore, although SARS-CoV-2 was not detected in the amniotic fluid, the possibility of vertical transmission could not be ruled out.

Intrapartum / post-partum infections

Since COVID-19 is transmitted mainly through respiratory droplets and by close contact, neonates could acquire the infection during delivery or post-partum. A study by Fan (Clin Inf Dis 2020, see ***below***) explored the topic of intrapartum transmission by testing vaginal secretions of COVID-19 infected mothers. They found vaginal swabs to be negative in all cases. Ferrazzi (BJOG 2020, see ***below***) investigated the possibility of transmission during vaginal delivery in 24 women. Of these 24 cases, only one newborn tested positive for the virus, presumably due to post-partum contamination. Liao (Int J Gynaecol Obstet 2020, see ***below***) found similar reassuring results. These findings may indicate that vaginal delivery does not increase the risk of viral transmission. The CDC therefore stated that COVID-19 infection is not an indication for delivery and states that vaginal delivery can be pursued in the event of spontaneous labour and good maternal condition.

Due to possible post-partum transmission of the disease, there has been discussion on whether or not to separate mother and newborn. Consensus guidance from China recommended routine separation of neonates from mothers infected by COVID-19 for at least 14 days (Chen Int J Gyn Obstetr 2020, see ***below***). During this period, direct breastfeeding was not recommended. However, routine precautionary separation of a mother and a healthy baby should not be undertaken lightly, given the potential detrimental effects on feeding and bonding. Furthermore, breastmilk contains specific antibodies with the capability of modulating an eventual SARS-CoV-2 infection in the newborn. In a document dated June 23 2020, WHO recommended that mothers with suspected or confirmed COVID-19 should be encouraged to initiate or continue to breastfeed (https://www.who.int/news-room/commentaries/detail/breastfeeding-and-covid-19). Mothers should be counselled that the benefits of breastfeeding substantially outweigh the potential risks for transmission. Mother and infant should be enabled to remain together while rooming-in throughout the day and night and to practice skin-to-skin contact, including

kangaroo mother care, especially immediately after birth and during establishment of breastfeeding, whether they or their infants have suspected or confirmed COVID-19.

Case definition

Interim case definitions based on the current information available have been issued by WHO (https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov)). The latest version of the document is dated August 7. The case definitions for suspected and probable cases have been revised as compared to earlier versions, to account for updated evidence on the most common or predictive symptoms and clinical and radiographic signs present in COVID-19 as well as known transmission dynamics. The current case definition integrates recent knowledge on signs and symptoms of COVID-19 issued from:

- publications describing the clinical spectrum of COVID-19 among hospitalized (e.g., Guan NEJM 2020, see ***below***; Menni 2020, see ***below***) and non-hospitalized (e.g., Spinato JAMA 2020, see ***below***; Tostamnn 2020, Struyf Cochrane Database Syst Rev 2020, see ***below***) COVID-19 patients and WHO Clinical management of COVID-19
- WHO's and partners' analysis of sensitivity, specificity and predictive value of most described signs and symptoms using surveillance data
- expert consultations with clinicians, radiologists and laboratory scientists connected to global expert networks who supported validation of the definition.

Of note, it has been recognized that countries may need to adapt COVID-19 case definitions depending on their local epidemiological situation and other factors.

Suspected case

A. A person who meets the clinical AND epidemiological criteria:
Clinical criteria:
1. Acute onset of fever AND cough;
OR
2. Acute onset of ANY THREE OR MORE of the following signs or symptoms: fever, cough, general weakness/fatigue1, headache, myalgia, sore throat, coryza, dyspnoea, anorexia/nausea/vomiting, diarrhoea, altered mental status.
AND
Epidemiological criteria:
1. Residing or working in an area with high risk of transmission of the virus: for example, closed residential settings and humanitarian settings, such as camp and camp-like settings for displaced persons, any time within the 14 days prior to symptom onset;
OR
2. Residing in or travel to an area with community transmission2 anytime within the 14 days prior to symptom onset;
OR
3. Working in health setting, including within health facilities and within households, anytime within the 14 days prior to symptom onset.

B. A patient with severe acute respiratory illness (SARI: acute respiratory infection with history of fever or measured fever of ≥ 38 C°; and cough; with onset within the last 10 days; and who requires hospitalization).

Probable case

A. A patient who meets clinical criteria above AND is a contact of a probable or confirmed case, or epidemiologically linked to a cluster of cases which has had at least one confirmed case identified within that cluster.

*B. A suspected case (described above) with chest imaging showing findings suggestive of COVID-19 disease**

** Typical chest imaging findings suggestive of COVID-19 include the following (Manna 2020):*
• chest radiography: hazy opacities, often rounded in morphology, with peripheral and lower lung distribution
• chest CT: multiple bilateral ground glass opacities, often rounded in morphology, with peripheral and lower lung distribution
• lung ultrasound: thickened pleural lines, B lines (multifocal, discrete, or confluent), consolidative patterns with or without air bronchograms.

C. A person with recent onset of anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identified cause.

D. Death, not otherwise explained, in an adult with respiratory distress preceding death AND who was a contact of a probable or confirmed case or epidemiologically linked to a cluster which has had at least one confirmed case identified within that cluster.

Confirmed case
A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Death due to COVID-19
A COVID-19 death is defined for surveillance purposes as a death resulting from a clinically compatible illness in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (e.g. trauma). There should be no period of complete recovery between the illness and death.

Definition of severe disease

While WHO has not provided a definition of severe cases of COVID-19, various publications have classified disease cases according to severity. For instance, Zhang (Allergy 2020, see ***below***) designated severe COVID-19 when the patients had one of the following criteria: 1) Respiratory distress with respiratory frequency ≥ 30/min; 2) Pulse Oximeter Oxygen Saturation ≤ 93% at rest; 3) Oxygenation index (artery partial pressure of oxygen/inspired oxygen fraction, PaO2/FiO2) ≤ 300 mmHg. Critical cases have also been defined as having respiratory failure, septic shock, and/or multiple organ dysfunction or failure (with fatal cases reported only in the last group) (Wu JAMA 2020, see ***below***).

Pathophysiology of COVID-19

The pathogenesis of COVID-19 is under investigation. Of note, a review on the comparative pathogenicity of the different human coronaviruses was published by Liu (J Med Vir 2020, see ***below***).

Viral tropism

The S protein is responsible for coronavirus entry into the cell after by binding to a cell receptor and membrane fusion, two key steps in viral infection and pathogenesis (Benvenuto J Med Vir 2020, see ***below***). Virus infectivity studies using HeLa cells expressing or not expressing ACE2 proteins from humans, Chinese horseshoe bats, civet, pig, and mouse showed that SARS-CoV-2 is able to use all but mouse ACE2 as an entry receptor in ACE2-expressing cells, but not cells without ACE2. ACE2 therefore appears as the likely cell receptor of SARS-CoV-2 (Zhou Nature 2020, see ***below***). It was also demonstrated that SARS-CoV-2 does not use other coronavirus receptors, aminopeptidase N and dipeptidyl peptidase 4.

However, cell entry of coronaviruses depends not only on binding of the viral S proteins to cellular receptors but also on S protein priming by host cell proteases. Hoffmann (Cell 2020, see ***below***) demonstrated that SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming.

ACE2 is expressed in a variety of cells of different organs (endothelium, liver, lungs, etc.) and is part of the renin-angiotensin blood pressure regulation system. In the respiratory tract, it is expressed on the apical face of respiratory epithelial cells via which infection may be mediated. Along the respiratory tract, ACE2 has been detected in the trachea, main bronchus and alveoli, and occasionally also in the small bronchi. An expression study found that ACE2 was mostly (83%) expressed by type II alveolar cells (AT2), and that this cell population also highly expressed other genes that positively regulate viral reproduction and transmission (Zhao Am J Respir Crit Care Med 2020, see ***below***).

By single cell sequencing, Weng (on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.02.08.926006v3.full) found a strong co-expression between ACE2 and TMPRSSs, especially TMPRSS1 and TMPRSS2, in lung AT2 cells, which was also the main infected cell type in SARS-CoV pneumonia. Moreover, he found the endocytosis-associated genes were highly expressed in AT2 cells, implying that endocytosis may also facilitate the entry of SARS-CoV-2 into host cells. As the alveolar stem-like cells, AT2 cells promote surfactant biosynthesis, self-renewal and immunoregulation. Thus, SARS-CoV-2 appears to not only damage the AT2 cells leading to the direct injury to alveoli, but also raise alveolar surface tension to induce dyspnoea.

Lukassen (EMBO J 2020, see ***below***) investigated virus infection in the respiratory tract. SARS-CoV-2 was reported to enter cells via binding to ACE2, followed by its priming by TMPRSS2. ACE2 was found predominantly expressed in a transient secretory cell type in the subsegmental bronchial branches. Interestingly, these transiently differentiating cells show an enrichment for pathways related to RHO GTPase function and viral processes suggesting increased vulnerability for SARS-CoV-2 infection.

Based on the public single-cell RNA-Seq datasets, Wu (https://www.medrxiv.org/content/10.1101/2020.02.11.20022228v2) found ACE2 expression in nasal epithelial cells. The size of this population of ACE2-expressing nasal epithelial cells appeared comparable with the size of the population of ACE2-expressing AT2 cells.

Using bulk RNA-seq profiles from two public databases and single-cell transcriptomes from an independent dataset generated in-house, Xu (Int J Oral Sci 2020, see ***below***) found evidence of ACE2 expression in the oral cavity and suggested enrichment in epithelial cells. Moreover, among different oral sites, ACE2 expression was found higher in tongue than buccal and gingival tissues.

ACE2 and TMPRSSs are also highly co-expressed in absorptive enterocytes and upper epithelial cells of oesophagus, implying that intestinal epithelium and oesophagus epithelium may also be the potential target tissues. Liang (Gut 2020, see ***below***) also reported that ACE2 mRNA was highly expressed in the healthy human small intestine. Besides, single-cell RNA sequencing data showed ACE2 to be significantly elevated in proximal and distal enterocytes. Zhou (Nat Med 2020, see ***below***) demonstrated active replication of SARS-CoV-2 in human intestinal organoids and isolation of infectious virus from the stool specimen of a patient with diarrheal COVID-19. The robust SARS-CoV-2 replication in human intestinal organoids suggests that the human intestinal tract might be a transmission route of SARS-CoV-2. They also established the first expandable organoid culture system of bat intestinal epithelium and present evidence that SARS-CoV-2 can infect bat intestinal cells.

In addition, a manuscript by Lin (https://www.biorxiv.org/content/10.1101/2020.02.08.939892v1) reported the use of published kidney and bladder cell atlas data and an independent unpublished kidney single cell RNA-Seq data to evaluate ACE2 gene expressions in all cell types in healthy kidneys and bladders. Results showed the enriched expression of all subtypes of proximal tubule cells of kidney and low but detectable levels of expression in bladder epithelial cells. The data suggest that the urinary system may be a potential target for infection. Fan (on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.12.20022418v1) also noted that ACE2 is highly expressed in renal tubular cells, Leydig cells and cells in seminiferous ducts in testis. The authors recommended renal function evaluation

and special care of patients, especially in case of therapy with drugs associated with renal toxicity, and suggested that clinicians should pay attention to the risk of testicular lesions in patients. However, this hypothesis was not supported by the observations by Wang (see ***Clinical disease in China*** above).

Liu (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.28.20029181v1), using public datasets (bulk RNA-seq and single-cell RNA-seq), showed expression of ACE2 in pancreas (in both exocrine glands and islets), and related this observation to clinical data suggesting mild pancreatitis in some patients. Among 67 severe cases, 11 patients (16.41%) showed elevated levels of both amylase and lipase, and 5 patients (7.46%) showed imaging alterations.

To construct a risk map of different human organs, Zou (Front Med 2020, see ***below***) analysed the single-cell RNA sequencing (scRNA-seq) datasets derived from major human physiological systems, including the respiratory, cardiovascular, digestive, and urinary systems, for ACE2 expression. Through scRNA-seq data analyses, the authors identified the organs at risk, such as lung, heart, oesophagus, kidney, bladder, and ileum, and located specific cell types (i.e., type II alveolar cells (AT2), myocardial cells, proximal tubule cells of the kidney, ileum and oesophagus epithelial cells, and bladder urothelial cells) as vulnerable to SARS-CoV-2 infection.

Chen (manuscript available on Preprints: https://www.preprints.org/manuscript/202002.0258/v2) found that ACE2 expression in the lung increases with age. A high viral load in elderly patients could therefore be associated not only with low immunity but also with high expression of the ACE2 receptor. This could explain the high degree of severe disease in older patients with SARS-CoV-2 (Chen and Li Lancet Inf Dis 2020, see ***below***).

Considering that a conserved RGD (403-405:Arg-Gly-Asp) motif is present in the receptor -binding domain of the S proteins of all SARS-CoV-2, Sigrist (Antivir Res 2020, see ***below***) presented the hypothesis that SARS-CoV-2 acquired integrin-binding to promote virus entry into host cells. However, experimental proof of this is required. Binding to integrin may play a supplemental role to ACE2 binding, like facilitating endocytosis by signalling through the integrin. Alternatively, the virus could infect different target cells by binding to ACE2 or to integrins.

Using SARS-CoV-2 S protein pseudovirus system, Ou (Nature Comm 2020, see ***below***) confirmed that human ACE2 is the receptor for SARS-CoV-2, found that SARS-CoV-2 enters 293/hACE2 cells mainly through endocytosis, and that PIKfyve, TPC2, and cathepsin L are critical for entry.

Of note, a review by Li (Pharmacol Res 2020, see ***below***) provided an interesting summary on ACE2 expression. It presents for instance the influence of sex hormones, age, or diet on expression.

Portal of entry

Xu (J Dent Res 2020, see ***below***) analysed the expression of ACE2 in human organs in the GTEx portal. The expression of ACE2 in minor salivary glands was higher than that in lungs, which suggests salivary glands could be potential target for COVID-19. In addition, SARS-CoV RNA has been detected in saliva before lung lesions appeared. A similar phenomenon could explain the presence of asymptomatic infections with COVID-19.

Using *ex vivo* and *in vitro* culture systems, Hui (Lancet Respir Med 2020, see ***below***) found that the conjunctival epithelium and conducting airways appear to be potential portals of infection for SARS-CoV-2. SARS-CoV-2 infected ciliated, mucus-secreting, and club cells of bronchial epithelium, type 1 pneumocytes in the lung, and the conjunctival mucosa. In the bronchus, SARS-CoV-2 replication competence was higher than SARS-CoV. In the lung, SARS-CoV-2 replication was similar to SARS-CoV. In conjunctiva, SARS-CoV-2 replication was greater than SARS-CoV.

Determinants of pathogenicity

While information pertaining to the replication of SARS-CoV-2, and the interactions between the virus and its host, is accumulating, available data to document the mechanisms involved during infection by other human CoVs may also be of use (see for instance, Fung Ann Rev Microbiol 2019 ***below*** or Chen J Med Virol 2020 ***below***).

S protein and interaction with ACE2

The expression level and expression pattern of human ACE2 in different tissues might be critical for the susceptibility, symptoms, and outcome of SARS-CoV-2 infection. A single-cell RNA-sequencing (RNA-seq) analysis indicated that Asian males may have higher expression of ACE2. Cao (Cell Discov 2020, see ***below***) analysed coding-region variants in ACE2 and the expression quantitative trait loci (eQTLs) variants, which may affect the expression of ACE2, to compare the genomic characteristics of ACE2 among different populations. No direct evidence was identified genetically supporting the existence of S-protein binding-resistant ACE2 mutants in different populations. However, East Asian populations were found to have higher allele frequencies in the eQTL variants, associated with higher ACE2 expression in tissues, which may suggest different susceptibility or response to SARS-CoV-2 from different populations under similar conditions.

Subsequently, Hussain (J Med Vir 2020, see ***below***) found that ACE2 alleles, rs73635825 (S19P) and rs143936283 (E329G) showed noticeable variations in their intermolecular interactions with the viral S protein. These data provide a structural basis of potential resistance against SARS-CoV-2 infection driven by ACE2 allelic variants.

A manuscript by Meng (on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.02.08.926006v3.full) suggested enhanced S protein cleavage with SARS-CoV-2 compared to SARS-CoV. A SPRR insertion in the S1/S2 protease cleavage sites of SARS-CoV-2 S protein was found to increase cleavage efficiency as assessed by protein sequence alignment and furin score calculation. Additionally, the insertion sequence facilitates the formation of an extended loop which was more suitable for protease recognition by homology modelling and molecular docking. Coutard (Antivir Res 2020, see ***below***) and Wang (Virol Sin 2020, see ***below***) also identified a peculiar furin-like cleavage site in the S protein of SARS-CoV-2, which is lacking in the other SARS-like CoVs. The authors hypothesised that this cleavage site may affect the viral cycle and pathogenicity. Shang (PNAS 2020, see ***below***) subsequently confirmed that unlike SARS-CoV, cell entry of SARS-CoV-2 is preactivated by proprotein convertase furin, reducing its dependence on target cell proteases for entry. The high hACE2 binding affinity of the RBD, furin preactivation of S, and hidden RBD in S potentially allow SARS-CoV-2 to maintain efficient cell entry while evading immune surveillance.

Through plaque purification of Vero-E6 cultured SARS-CoV-2, Lau (Em Micr Inf 2020, see ***below***) found a virus variant with in-frame deletions in the S1/S2 cleavage site region (Del-mut-1), which is attenuated in its ability to cause disease in a SARS-CoV-2 hamster model.

Increased receptor expression

A study by Ziegler (Cell 2020, see ***below***) demonstrated that the antiviral interferon response upregulates the expression of ACE2 in human nasal epithelia and lung tissue. This finding suggested that SARS-CoV-2 could exploit the interferon pathway, essential for host antiviral defence, to enhance infection.

Infection of immune cells

Xu (Int J Oral Sci 2020, see ***below***) found ACE2 expression in lymphocytes within the oral mucosa, and reported similar expression in various organs of the digestive system and in lung, even though the proportion of ACE2-positive lymphocytes was quite small.

Wang (Cell Mol Immunol. 2020, see ***below***) showed that SARS-CoV-2 could infect T cells (MT-2 cell line) and that infection occurred through receptor-dependent, S protein-mediated membrane fusion. A very low expression level of

hACE2 was found; from these data, the authors concluded that a novel receptor might mediate SARS-CoV-2 entry into T cells. However, the relevance of these data obtained in cell line to primary T cells remains to be confirmed.

In a study by Feng (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.03.27.20045427v1.full.pdf+html), spleens and lymph nodes from six COVID-19 patients with post-mortem examinations were collected and inspected for viral presence in resident macrophages, B cells and T cells. Immunochemistry demonstrated that SARS-CoV-2 nucleoprotein could be detected in ACE2+, CD169+ macrophages in spleen and lymph nodes, while no viral infection could be found in T cells and B cells. Moreover, it was observed that SARS-CoV-2 infection induces severe tissue damage including lymph follicle depletion, splenic nodule atrophy, histiocyte hyperplasia and lymphocyte reductions. The authors suggest that lymphocytopenia that is prevalent in COVID-19 patients might be caused by viral infected macrophages inducing lymphocyte apoptosis, mediated by Fas/FasL signalling.

Other observations

Angeletti (J Med Vir 2020, see ***below***) used sequence analysis and modelling to predict features of SARS-Cov-2 pathogenicity. He suggested that the stabilizing mutation falling in the endosome-associated-protein-like domain of the nsp2 protein could account for COVID-19 high transmission capability, while the destabilizing mutation in nsp3 proteins could suggest a potential mechanism differentiating COVID-19 from SARS.

Fahmi (Infect Genet Evol. 2020, see ***below***) showed that two non-structural proteins, NS7b and NS8, were exclusively conserved among SARS-CoV-2, βCoV_RaTG, and BatSARS-like Cov. NS7b and NS8 have previously been shown to affect immune response signalling in the SARS-CoV experimental model. Thus, the authors speculated that the properties of these accessory proteins, NS7b and NS8, in SARS-CoV-2 may affect its ability to infect humans.

Pathological observations from biopsies and autopsies

A manuscript by Tian (J Thorac Oncol 2020, see ***below***) described examinations of biopsies of 2 asymptomatic cancer patients who underwent surgery and were later found to have been infected with SARS-CoV-2. The lungs of both patients exhibited oedema, proteinaceous exudate with globules, focal hyperplasia of pneumocytes with only patchy inflammatory cellular infiltration, and multinucleated giant cells. Hyaline membranes were not prominent. These observations likely represent an early phase of the lung pathology of COVID-19 pneumonia.

Xu (Lancet Resp Med 2020, see ***below***) described for the first time pathology findings from biopsies collected at autopsy. The pathological features of COVID-19 greatly resemble those seen in SARS and MERS. In addition, the liver biopsy specimens of the patient with COVID-19 showed moderate microvascular steatosis and mild lobular and portal activity, indicating the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury. There were a few interstitial mononuclear inflammatory infiltrates, but no other substantial damage in the heart tissue.

Zhang (Ann Int Med 2020, see ***below***) presented the histopathologic changes seen on post-mortem transthoracic needle biopsies from a patient with COVID-19 who had respiratory failure and radiographic bilateral ground-glass opacities. Nonspecific findings consistent with diffuse alveolar damage were observed. Immunostaining of lung sections with an antibody to the Rp3 N protein of SARS-CoV-2 revealed prominent expression on alveolar epithelial cells, including damaged, desquamated cells within the alveolar space. In contrast, viral protein expression was minimally detectable on blood vessels or in the interstitial areas between alveoli.

Barnes (J Exp Med 2020, see ***below***) studied the function of neutrophils and their ability to form neutrophil extracellular traps (NETs), which may contribute to organ damage and mortality in COVID-19. The authors showed lung infiltration of neutrophils in an autopsy specimen from a patient who succumbed to COVID-19. Prior reports extensively linked aberrant NET formation to pulmonary diseases, particularly ARDS. Intravascular NETs have been

shown to play a vital role in initiating and accreting thrombosis in arteries and veins. NETs may also be involved in the cytokine storm.

Menter (Histopathology 2020, see ***below***) reported autopsy findings of 21 COVID-19 patients hospitalised in Switzerland. The primary cause of death was respiratory failure with exudative diffuse alveolar damage with massive capillary congestion often accompanied by microthrombi despite anticoagulation. Ten cases showed superimposed bronchopneumonia. Further findings included pulmonary embolisms (n=4), alveolar haemorrhage (n=3) and vasculitis (n=1). Pathologies in other organ systems were predominantly attributable to shock; three patients showed signs of generalised thrombotic microangiopathy. Six patients were diagnosed with senile cardiac amyloidosis upon autopsy. Most patients suffered from one or more comorbidities (hypertension, obesity, cardiovascular diseases, diabetes mellitus).

Mechanisms of enhanced disease

Antibody-dependent enhancement (ADE) occurs when antibodies facilitate viral entry into host cells and enhance viral infection in these cells. ADE has been observed for a variety of viruses, most notably flaviviruses (e.g., dengue virus). ADE has been observed for coronaviruses. Several studies have shown that sera induced by SARS-CoV S enhance viral entry into Fc receptor-expressing cells, including monocytes, macrophages and B cells (Wan, Shang, Sun et al. J Vir 2020, see ***below***). One study demonstrated that unlike receptor-dependent viral entry, serum-dependent SARS-CoV entry does not go through the endosome pathway. Additionally, it has long been known that immunization of cats with feline coronavirus S leads to worsened future infection due to the induction of infection-enhancing antibodies. Wan et al. further studied the molecular mechanism of ADE using MERS-CoV and a monoclonal antibody as a model.

As early as in February 2020, a publication by Tetro (Micr Inf 2020, see ***below***) further described the hypothesis that ADE due to prior exposure to other coronaviruses could underlie the severity of cases in the Hubei province. In the context of identifying the priming coronavirus, the authors noted that as the introduction of SARS-CoV into humans has been suggested to have occurred in the Hubei Province. However, SARS-CoV is not likely to be a predominant priming virus for ADE to SARS-CoV-2. Seroprevalence studies have shown a very low level of SARS-CoV seroconversion in the population apart from workers with direct contact with animals such as traders.

Alternatively, Fu (Virol Sin 2020, see ***below***) speculated that a mechanism of ADE of viral infection occurs in some patients with early, sub-optimal antibody activity that cannot completely clear the virus, but instead leads to persistent viral replication and inflammation.

A review by Iwasaki (Nature Rev Immunol 2020, see ***below***) outlined the potential danger of suboptimal antibody responses against SARS-CoV-2 and ADE, as well as implications for vaccine development. The authors raised the point that ADE might not facilitate the spread of SARS-CoV in infected hosts, as infection of macrophages through ADE does not result in productive viral replication and shedding. Instead, based on prior evidence with SARS-CoV, they suggest that non-neutralizing antibodies can promote inflammation and tissue injury by activating myeloid cells via FcRs. Enhanced disease might occur when low quality, low quantity antibodies are present, activating molecular mechanisms (e.g., FcR activation, viral RNA detection in macrophages, complement activation) that result in pro-inflammatory cytokine secretion, increased neutrophil and eosinophil lung infiltration, and more severe lung pathology. The conclusion of this paper referred to 2 manuscripts on medRxiv, which have associated higher titres of anti-S and/or anti-N IgG and IgM at all time points following the onset of symptoms with a worse disease outcome.

Zohar (Nat Rev Imm 2020, see ***below***) further described the possible role of complement in disease severity in COVID-19. Over-activation of the complement cascade by SARS-CoV-2 N, via the lectin pathway, has been reported to result in enhanced lung injury in mice. This study also showed that adding N-directed neutralizing monoclonal antibodies reduced fatality rates and lung injury. In addition to FcR expression, nearly all innate immune cells also express

complement receptors, providing an additional avenue through which antibodies may activate and direct the immune system. However, whether elevated antibody titres in progressive disease drive or temper complement activation remains to be determined.

Based on developing scientific data, ADE concerns with COVID-19 seem to have evolved over time. As noted by Yager (Clin Imm 2020, see ***below***), concerns of ADE with SARS-related coronaviruses are based primarily on experimental data with limited clinical evidence. As aging is associated with T-cell dysfunction, a role for aberrant T cell responses in elderly patients with severe disease should not be excluded. Further, aging is characterized by heightened, low-grade chronic inflammation. The presence of pre-existing antibodies against coronaviruses in patients is plausible. However, discordance between the epidemiology of severe COVID-19 cases and seroprevalence data for homologous βCoVs, and the fluctuating circulation patterns of analogous human coronaviruses, cast doubts on roles for cross-reactive antibodies in pathology. In a PNAS news feature (see ***below***), Peeples also noted that a pathogenic Th2 memory response with eosinophil and immune complex formation may cause (vaccine) enhanced disease.

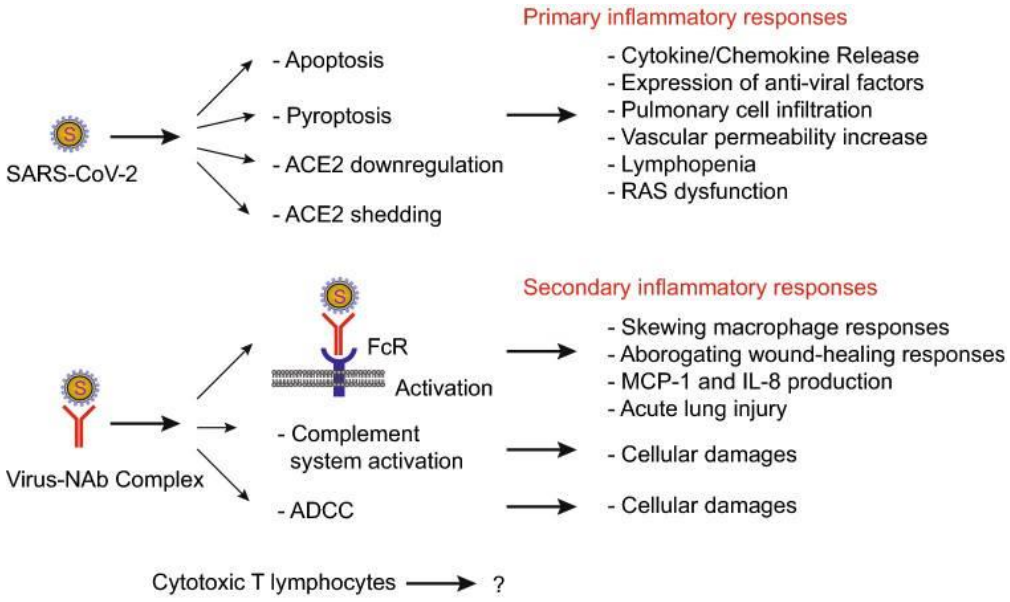
Arvin (Nature 2020, see ***below***) reviewed observations relevant to the risks of ADE of disease, and their potential implications for SARS-CoV-2 infection. At present, there are no known clinical findings, immunological assays or biomarkers that can differentiate any severe viral infection from immune-enhanced disease, whether by measuring antibodies, T cells or intrinsic host responses. *In vitro* systems and animal models do not predict the risk of ADE of disease, in part because protective and potentially detrimental antibody-mediated mechanisms are the same, and designing animal models depends on understanding how antiviral host responses may become harmful in humans. The authors suggested that comprehensive studies are urgently needed to define clinical correlates of protective immunity against SARS-CoV-2. Moreover, because ADE of disease cannot be reliably predicted after either vaccination or treatment with antibodies, it will be essential to depend on careful analysis of safety in humans as immune interventions for COVID-19 move forward.

Hyperinflammation and acute respiratory distress syndrome

Similar to patients with SARS-CoV and MERS-CoV, patients with COVID-19 have soon been observed to develop acute respiratory distress syndrome (ARDS) with characteristic pulmonary ground glass changes on imaging (Zumla Lancet 2020, see ***below***). COVID-19 is also associated with increases in IL-6, IL-10, IL-2 and IFN-γ levels in the peripheral blood in the severe cases compared to those in the mild cases (Liu EBioMed 2020, see ***below***). Evidence has rapidly accumulated to indicate that part of the severe COVID-19 patients have an elevated cytokine profile resembling the cytokine storm described in SARS and MERS (Zhang Clin Imm, see ***below***). The observations have been found consistent with the characteristics of the so called “primary cytokine” storm induced by viral infection which were mainly produced by alveolar macrophages, epithelial cells and endothelial cells, rather than those observed in “secondary cytokine” storm induced by different subsets of activated T lymphocytes in late stage of viral infection or a complication of T cell-engaging therapies.

Fu (Virol Sin 2020, see ***below***) explored the possible mechanisms of the inflammatory response observed in COVID-19 pneumonia. Based on previous studies of SARS-CoV, he separated the inflammatory responses in SARS-CoV-2 infection into primary and secondary responses (***Figure 11***). Primary inflammatory responses occur early after viral infection, prior to the appearance of neutralizing antibodies (NAb). These responses are mainly driven by active viral replication, viral-mediated ACE2 downregulation and shedding, and host antiviral responses. Secondary inflammatory responses begin with the generation of adaptive immunity and NAb. The virus-NAb complex can also trigger FcR-mediated inflammatory responses and acute lung injury.

Figure 11 Possible mechanisms of SARS-CoV-2-mediated inflammatory responses (from Fu Virol Sin 2020).



Interestingly, Ong (Cell Host & Microbe 2020, see ***below***) found a highly dynamic expression of pro-inflammatory genes in COVID-19. Expression of most of these genes peaked after nadir of respiratory function, which questions a cytokine storm hypothesis. Instead the authors' data hints at the possibility that the IL1 pathway may be a more suitable correlate of severe respiratory disease.

The cytokine profile associated with COVID-19 disease severity has been reported as characterised by increased IL-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumour necrosis factor-α. Predictors of fatality have been found to include elevated ferritin and IL-6, suggesting that mortality might be due to virally driven hyperinflammation (Mehta Lancet 2020, see ***below***).

A better description of how the immune cell landscape is perturbed in severe COVID-19 was recently provided by Xu (Cell Discov 2020, see ***below***). Using single-cell RNA sequencing, the authors characterized the peripheral blood mononuclear cells (PBMCs) from uninfected controls and COVID-19 patients and cells in paired broncho-alveolar lavage fluid (BALF). They found a close association of decreased dendritic cells (DCs) and increased monocytes resembling myeloid-derived suppressor cells (MDSCs), which correlated with lymphopenia and inflammation in the blood of severe COVID-19 patients. Those MDSC-like monocytes were immune-paralyzed. In contrast, monocyte-macrophages in BALFs of COVID-19 patients produced massive amounts of cytokines and chemokines, but secreted little interferons. The frequencies of peripheral T cells and NK cells were significantly decreased in severe COVID-19 patients, especially for innate-like T and various CD8+ T cell subsets, compared to healthy controls. In contrast, the proportions of various activated CD4+ T cell subsets among the T cell compartment, including Th1, Th2, and Th17-like cells were increased and more clonally expanded in severe COVID-19 patients. Patients' peripheral T cells showed no sign of exhaustion or augmented cell death, whereas T cells in BALFs produced higher levels of IFNG, TNF, CCL4, CCL5, etc. Paired TCR tracking indicated abundant recruitment of peripheral T cells to the severe patients' lung.

Ciceri (Crit Care Resusc 2020, see ***below***) suggested "MicroCLOTS" (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) as a new name for severe pulmonary COVID-19. The authors hypothesised that, in predisposed individuals, alveolar viral damage is followed by an inflammatory reaction and by microvascular pulmonary thrombosis. This progressive endothelial thromboinflammatory syndrome may also involve the microvascular bed of the brain and other vital organs, leading to multiple organ failure and death.

Magro (Transl Res 2020, see ***below***) examined skin and lung tissues from 5 patients with severe COVID-19 characterized by respiratory failure (n=5) and purpuric skin rash (n=3) by light microscopy and immunohistochemistry. No viral cytopathic changes were observed and the diffuse alveolar damage with hyaline membranes, inflammation, and type II pneumocyte hyperplasia, hallmarks of classic ARDS, were not prominent. These pulmonary findings were accompanied by significant deposits of terminal complement components C5b-9 (membrane attack complex), C4d, and MASP2, in the microvasculature, consistent with sustained, systemic activation of the alternative and lectin-based complement pathways. The purpuric skin lesions similarly showed a pauci-inflammatory thrombogenic vasculopathy, with deposition of C5b-9 and C4d in both grossly involved and normally-appearing skin. In addition, there was co-localization of COVID-19 spike glycoproteins with C4d and C5b-9 in the inter-alveolar septa and the cutaneous microvasculature of two cases examined. In conclusion, at least a subset of sustained, severe COVID-19 may define a type of catastrophic microvascular injury syndrome mediated by activation of complement pathways and an associated procoagulant state.

Impact of age on disease severity

Molloy (Pediatr Res 2020, see ***below***) suggested that a possible reason for the disparity in severity between adults and children may relate to differences in receptors in the renin-angiotensin system and altered inflammatory responses to pathogens. The differences in immune responses to SARS-CoV-2 in hospitalized paediatric and adult patients were analysed by Pierce (Sci Transl Med 2020, see ***below***) to identify potential contributing mechanisms. In the first week after hospitalization, circulating IL-17A and IFN-γ concentrations were inversely related to age. More than 3 weeks later, CD4+ T cell responses to S protein were higher in adult compared to younger patients. Neutralizing antibody titres were also higher in adults and correlated positively with age and negatively with IL-17A and IFN-γ. These findings suggest that the poor outcome in adults is not caused by a failure to generate adaptive immune responses.

Influence of gender

A review by Scully (Nat Rev Imm 2020, see ***below***) introduced sex-differential features of immunity and highlighted the potential sex differences underlying COVID-19 severity. In one cohort of patients with COVID-19, severe respiratory failure was associated with a pattern of inflammation, macrophage activation and depletion of lymphocytes that was distinct from bacterial infection. There was a sex bias for severe COVID-19 not observed in the comparator group with bacterial infections. Sex-differential production of IL-6, monocyte transcriptional patterns and inflammatory set point could contribute to an enhanced risk of death in males.

Mechanisms of myocardial injury

Both Guo (JAMA Cardiol 2020, see ***below***) and Shi (JAMA Cardiol 2020, see ***below***) observed that myocardial injury is significantly associated with fatal outcome of COVID-19 in China. A review of the importance of myocarditis in COVID-19 was published by Madjid (JAMA Cardiol 2020, see ***below***), who suggested that myocardial injury is likely associated with infection-related myocarditis and/or ischemia, and provides an important prognostic factor in COVID-19. Bonow (JAMA Cardiol 2020, see ***below***) further discussed the observation that patients with pre-existing cardiovascular disease are susceptible to the most adverse complications of COVID-19, and the fact that the mechanisms responsible for these outcomes remain largely unknown. Bonow also pointed to a mechanism of demand ischemia that devolves into myocardial injury or plaque disruption stimulated by intense systemic inflammatory stimuli. SARS-CoV-2 can elicit an intense release of multiple cytokines and chemokines that may lead not only to vascular inflammation and plaque instability but also to myocardial inflammation. Direct viral infection of the myocardium is another possible causal pathway of myocardial damage. The affinity of SARS-CoV-2 for the host ACE2 receptor also raises the possibility of direct viral infection of vascular endothelium and myocardium. It is thus possible that in some patients with or without pre-existing cardiovascular disease, COVID-19-associated myocardial injury could represent myocarditis.

Chen (Cardiovasc Res 2020, see ***below***) found that pericytes with high expression of ACE2 might act as the target cardiac cell of SARS-CoV-2. The pericytes injury due to virus infection may result in capillary endothelial cells

dysfunction, inducing microvascular dysfunction. Patients with basic heart failure disease showed increased ACE2 expression at both mRNA and protein levels, meaning that if infected by the virus these patients may have higher risk of heart attack and critically ill condition. This study may explain the high rate of severe cases among COVID-19 patients with basic cardiovascular disease

Signs of liver injury

Guan (Zhonghua Gan Zang Bing Za Zhi 2020, see ***below***) investigated the possible mechanism of liver injury in patients. ALT and AST are indeed abnormally elevated in some patients, especially in severe disease cases. The author assumed that in addition to the over-activated inflammatory response in patients with COVID-19 pneumonia, the up-regulation of ACE2 expression in liver tissue caused by compensatory proliferation of hepatocytes derived from bile duct epithelial cells may also be the possible mechanism of liver tissue injury.

A publication by Xu (Liver Int 2020, see ***below***) provided a summary of available information on SARS-CoV-2 and liver injury. The authors noted that the liver injury observed in COVID-19 patients might be caused by lopinavir/ritonavir, and that there is still a lack of reports that liver failure occurs in COVID-19 patients with chronic liver diseases.

Neurotropism

Li, Bai et Hashikawa (J Med Vir 2020, see ***below***), considering the similarities of the disease with SARS-CoV and MERS-CoV, proposed a potential neuroinvasion of SARS-CoV-2 to be partially responsible for the acute respiratory failure of COVID-19 patients. A similar hypothesis has been raised by Steardo (Acta Physiol 2020, see ***below***).

Conde Cardona (J Neurol Sci 2020, see ***below***) presented a series of arguments supporting the contention that that respiratory distress is not only the result of pulmonary inflammatory structural damage, but also due to the damage caused by the virus in the respiratory centers of the brain. These arguments included for instance the neurological symptoms observed in a subset of the patients (incl. anosmia and dysgeusia), detection of the virus genome in the cerebrospinal fluid of a patient, as well as presence of receptors of ACE2 in the cerebral vascular endothelium and its self-regulatory function, causing elevation of cerebral blood pressure.

Co-infections

Since the beginning of the epidemic, various authors have observed co-infections with SARS-CoV-2 and another pathogen. For instance, a study by Wang (manuscript on medRxiv : https://www.medrxiv.org/content/10.1101/2020.02.12.20022327v2) analysed 613 patients with fever who underwent multiple tests for 13 respiratory pathogens. Interestingly, 5.8% of patients with SARS-CoV-2 infection were reported to be co-infected with coronavirus (3/104), influenza A virus (2/104), rhinovirus (2/104), and/or influenza A H3N2 (1/104).

Similarly, respiratory virus, fungi and bacteria co-infections were reported by Ai (on medRxiv https://www.medrxiv.org/content/10.1101/2020.02.13.20022673v1).

A case report on co-infection with SARS-CoV-2 and Influenza A Virus in a patient with pneumonia in China has also been presented (Wu Emerg Inf Dis 2020, see ***below***).

Lin (Sci China Life Sci 2020, see ***below***) reported on the use of a multiplex RT-PCR method (multiplex rapid detection kit 2.0, Uni-MEDICA Tech, Shenzhen), which can simultaneously detect 15 respiratory tract infection pathogens including the SARS-CoV-2, was employed to screen the pathogen agents in the patients. These 15 respiratory pathogens are SARS-CoV-2, influenza A/B, coronavirus NL63, coronavirus, parainfluenza virus type 1/2/3(PIV1/2/3), adenovirus, rhinovirus (hRV), human bocavirus, coronavirus HKU1 (HKU1), coronavirus OC43, human metapneumovirus (hMPV) and respiratory syncytial virus (RSV). A total of 186 suspected COVID-19 cases were tested. In the 92 SARS-CoV-2 (49.46%) positive patients, the common respiratory viruses RSV, hRV, hMPV, PIV2 and HKU1

were also simultaneously detected in six patients (3.2%) respectively, of which four patients (2.2%) were positive for at least two detected viruses. The co-infections in these six patients were further verified in parallel testing using a second-day sampling from the same patients.

Zhu (J Med Vir 2020, see ***below***) reported on a severe case involving co-infection of SARS-CoV-2 and HIV. Unfortunately, the publication did not provide details as to the time of HIV diagnosis.

Rawson (Clin Inf Dis 2020, see ***below***) explored the current literature surrounding bacterial/fungal co-infection in patients with coronavirus infection. 62/806 (8%) COVID-19 patients were reported as experiencing bacterial/fungal co-infection during hospital admission. Secondary analysis demonstrated wide use of broad-spectrum antibacterials.

More recently, Lai (J Microbiol Immunol Infect 2020, see ***below***) reported that Aspergillus spp. can cause co-infections in patients with COVID-19, especially in severe/critical illness.

Animal models

Animal models are required to provide information on pathogenesis, host responses to infection, and to evaluate vaccines and other therapeutic targets (Cohen Science 2020b, see ***below***). In March 2020, Yuan (Em Micr Infect, see ***below***) provided a clear review on the status of natural and experimental infection of SARS-COVs and MERS in animal models.

On the basis of sequence analyses, Wan, Shang, Graham et al. (J Vir 2020, see ***below***) predicted that either SARS-CoV-2 or laboratory mice and rats would need to be genetically engineered before a robust mouse or rat model for COVID-19 would become available. By contrast, the authors noted that pigs, ferrets, cats, and non-human primates contain largely favourable SARS-CoV-2 -contacting residues in their ACE2 and hence may serve as animal models for SARS-CoV-2. Comparison of SARS-CoV and SARS-CoV-2 S proteins bound the ACE2 receptors showed that the SARS-CoV-2 S glycoprotein has adapted to bind the human, but not rodent, ACE2 with high affinity and that ferrets are the most suitable model for the study of inhibitory antibodies and small molecules targeting the SARS-CoV-2 S protein interaction with ACE2 (Brooke, manuscript on Research Square: https://doi.org/10.21203/rs.3.rs-29443/v1). In contrast, the authors did not detect species-specific adaptation for TMPRSS2. Bosco-Lauth (manuscript on bioRxiv: https://doi.org/10.1101/2020.05.28.120998) studied the pathogenesis and SARS-CoV-2 transmission in domestic cats and suggested they may be an animal model more relevant to study mild human disease. Additionally, the relatively high-titer viral shedding produced by cats and the rapidity of transmission may make them an ideal model for simulation of aerosols. As such, cat models may be quite useful for understanding the shed/spread kinetics of SARS-CoV-2 furthering the development of vaccines and therapeutics.

Transgenic mice

Bao (Nature 2020, see ***below***) presented data supporting the suitability of the SARS-CoV transgenic mouse model for SARS-CoV2. The hACE2 transgenic mice were inoculated intranasally at a dosage of 10^5 TCID50 per mouse. Weight loss of up to 5% was observed for 10 dpi only in the infected mice. Other clinical symptoms were not observed. The typical histopathology was interstitial pneumonia with significant inflammatory cells infiltration around the bronchioles and blood vessels, and viral antigens were observed in bronchial epithelial cells and alveolar epithelial cells. The phenomenon was not found in wild type mice infected with SARS-CoV-2.

Sun (Cell Host Micr 2020, see ***below***) generated a mouse model expressing human ACE2 (hACE2) by using CRISPR/Cas9 knockin technology. In comparison with wild-type C57BL/6 mice, both young and aged hACE2 mice sustained high viral loads in lung, trachea, and brain upon intranasal infection. Although fatalities were not observed, interstitial pneumonia and elevated cytokines were seen in SARS-CoV-2 infected-aged hACE2 mice. Interestingly, intragastric

inoculation of SARS-CoV-2 was seen to cause productive infection and lead to pulmonary pathological changes in hACE2 mice.

The limited global availability of hACE2 transgenic mice led Israelow (J Exp Med 2020, see ***below***) to develop a mouse model of SARS-CoV-2 infection and pathogenesis by delivering human ACE2 (hACE2) into the respiratory tract of mice using adeno-associated virus (AAV). The AAV-hACE2 mice supported productive viral replication, mounted a significant antibody response, and developed acute inflammatory pulmonary pathology similar to that found in COVID-19 patients and non-human primate models. Assessment of the AAV-hACE2 mice's cytokine and interferon response to SARS-CoV-2 revealed clear signatures of cytokines and interferon stimulated genes (ISGs), but no upregulation of type I, II or III interferons. The majority (73%) of upregulated genes were ISGs, and a distinct subset of 45 genes elevated in the infected lung were specific to type I interferon signalling; this type of interferon signalling was responsible for recruitment of proinflammatory cells into the lungs and for ISG expression, but not for viral clearance. This was consistent with other reports of elevated interferon signatures in the lungs of COVID-19 patients, and suggests that these AAV-hACE2 mice represent a useful model for studies of SARS-CoV-2 infections in humans.

Golden Syrian Hamsters

Chan (Clin Infect Dis 2020, see ***below***) established a readily available small animal model for COVID-19 using golden Syrian hamster (*Mesocricetus auratus*). The Syrian hamster could be consistently infected by SARS-CoV-2. Within the first week of challenge, the following observations were made:

- Maximal clinical signs of rapid breathing, weight loss and postural changes
- Histopathological changes from the initial exudative phase of diffuse alveolar damage with extensive apoptosis to the later proliferative phase of tissue repair, airway and intestinal involvement with virus nucleocapsid protein expression,
- High lung viral load, with a titre between 10^5-10^7 TCID50/g, peaking on day 2 post-inoculation and remaining detectable beyond day 7.
- Spleen and lymphoid atrophy associated with marked cytokine activation.

Challenged index hamsters consistently infected naïve contact hamsters housed within the same cage, resulting in similar pathology but not weight loss. All infected hamsters recovered and developed mean serum neutralising antibody titre ≥1:427 fourteen days post-challenge. Immuno-prophylaxis with early convalescent serum achieved significant decrease in lung viral load but not in lung pathology.

Contrastingly, a more recent study demonstrated that SARS-CoV-2 replicates efficiently in the lungs of both young and older Syrian hamsters and causes severe pathological lesions in the lungs of these animals (Imai 2020 PNAS, see ***below***). By using in vivo X-ray microcomputed tomographic (micro-CT) imaging, they showed that severe lung injury occurs in infected hamsters and that the severity of the lung abnormalities is related to the infectious dose. Finally, they assessed whether primary infection or passive transfer of convalescent serum could suppress the replication of SARS-CoV-2 in hamsters. The levels of virus titer reduction were substantial in animals treated with convalescent sera (i.e., nearly 1,000-fold virus titer reduction in the lungs of animals inoculated with convalescent sera 1 d post-infection and nearly 100-fold virus titer reduction in those inoculated on day 2 post-infection).

Sia (Nature 2020, see ***below***) made similar observations and reported that SARS-CoV-2 was transmitted efficiently from inoculated hamsters to naive hamsters by direct contact and via aerosols. Transmission via fomites in soiled cages was not as efficient. Although viral RNA was continuously detected in the nasal washes of inoculated hamsters for 14 days, the communicable period was short and correlated with the detection of infectious virus but not viral RNA.

The age-related effects of COVID-19 observed in elderly human patients led Osterreider (Viruses 2020, see ***below***) to compare the effects of SARS-CoV-2 infections in younger (6 months of age) vs. older (32-34 months of age) golden

hamsters. Viral replication in the upper and lower respiratory tract of experimentally-inoculated hamsters was independent of age, however clear age-dependent differences were seen: older hamsters exhibited more pronounced and consistent weight loss, developed more conspicuous alveolar and perivascular oedema indicative of vascular leakage, and mounted a slower and weaker immune response in lung tissue than younger animals. In addition, younger animals demonstrated rapid lung recovery at 14 dpi, whereas older animals did not. The authors suggested that the age-dependent differences observed in Syrian hamsters, that appear to mirror those seen in human patients, may make them a valuable animal model for comparative assessments of COVID-19 vaccines and treatments (e.g. immunotherapies and antiviral drugs).

Ferrets

Kim (Cell Host Micr 2020, see ***below***) and Beer (ProMed archive number: 20200407.7196506) reported ferret models of SARS-CoV-2 infection and transmission that recapitulate aspects of human disease. SARS-CoV-2 infected ferrets exhibited elevated body temperatures and efficient virus replication in the upper respiratory tract (nasal turbinates, soft palate and tonsils) from as early as two days post-infection. Although fatalities were not observed, SARS-CoV-2-infected ferrets shed virus in nasal washes, saliva, urine and faeces for up to 8 days post-infection. At 2 days post-contact, SARS-CoV-2 was detected in all naïve direct contact ferrets. Furthermore, a few naïve indirect contact ferrets were positive for viral RNA, suggesting airborne transmission. Viral antigens were detected in nasal turbinate, trachea, lungs, and intestine with acute bronchiolitis present in infected lungs. Infections in ferrets appear to resemble mild human infections; this and the fact that SARS-CoV-2 replicates efficiently in the upper respiratory tract of ferrets makes them a candidate animal model for evaluating antiviral drugs or vaccine candidates against COVID-19.

As seen above, given their susceptibility to experimental infection and onward transmission via direct and indirect contact, ferrets have been proposed as an animal model to study SARS-CoV-2 transmission. However, interestingly, in a natural experiment where 29 ferrets in one home had prolonged, direct contact and constant environmental exposure to two humans with symptomatic COVID-19, no evidence of SARS-CoV-2 transmission into the household ferret population via RT-PCR and ELISA was observed. To better understand this discrepancy between experimental and natural infection in ferrets, Sawatzki (manuscript on bioRxiv : https://www.biorxiv.org/content/10.1101/2020.08.21.254995v2) compared SARS-CoV-2 sequences from natural and experimental mustelid infections. They analysed all currently available genomic sequences of SARS-CoV-2 viruses of naturally infected European minks and experimentally infected ferrets. Viral sequences available from the two natural reverse zoonotic events in European mink farms (see section ***Human to animal transmission and risk of reverse spillover*** for details) allowed to infer founder-effect mutations versus acquired mutations of relevance to spillover. The authors identified three mutations of interest in the S protein coding sequence: N501T, D614G and S686G associated with mustelids. While there is evidence that ACE2 provides a weak host barrier, one mutation only seen in ferrets is located in the novel S1/S2 cleavage site and is computationally predicted to decrease furin activity. The absence of transmission in the high-exposure home contrasts with multiple human-to-mink spillover events, suggesting additional host barriers specific to ferrets. To date, experimental ferret infections have been successful (6×10^5 and $10^{5.5}$ TCID50), and at least one inoculum contained a minority of virus with the S686G variant. These limitations may negatively affect ferrets as a disease and/or transmission model and should be further investigated.

Cynomolgus macaques

Rockx (Science 2020, see ***below***) compared the pathogenesis of COVID-19, MERS and SARS in cynomolgus or crab-eating macaques, and showed that SARS-CoV-2 infection in cynomolgus macaques results in COVID-19-like disease with prolonged virus excretion from nose and throat in absence of clinical signs. SARS-CoV-2 was introduced via combined intratracheal and intranasal inoculation; no significant weight loss or overt clinical signs were detected in any of the 8 macaques except for a serous nasal discharge in an aged animal on day 14 post-infection, by which time all remaining animals had seroconverted as identified by the detection of specific antibodies against the S1 domain

and N proteins of SARS-CoV-2. Higher levels of viral RNA were detected in nasal swabs of aged animals compared to younger animals. Viral replication was highest in lung tissue, but was also detected in ileum and tracheo-bronchial lymph nodes. In contrast, macaques infected with MERS-CoV via the same method remained free of clinical signs and seroconverted by day 21 post-infection; low levels of viral RNA were detected in nasal, throat and rectal swabs. The authors concluded that cynomolgus macaques are permissive to SARS-CoV-2 infection, shed virus for pronged periods of time, and display COVID-19-like disease. Severity of disease appeared to be intermediate between SARS-CoV and MERS-CoV infections established by similar inoculation doses and routes.

Rhesus macaques

Lu (manuscript on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.04.08.031807v2) compared experimental inoculation of three non-human primate species with SARS-CoV-2. The study indicated that rhesus macaques (*Macaca mulatta*) were the most susceptible to SARS-CoV-2 infection, followed by cynomolgus or crab-eating macaques (*Macaca fascicularis*) and lastly common marmosets (*Callithrix jacchus).* Increased body temperature was continuously recorded in 100% (12/12) of Rhesus macaques, 33.3% (2/6) of crab-eating macaques and 0% (0/6) of common marmosets. Weight loss and radiographic chest abnormalities were observed in rhesus macaques and crab-eating macaques, but were not performed in common marmosets. Viral genome was detected in nasal, throat and anal swabs as well as in blood from all three monkey species, with viral shedding from the upper respiratory tract peaking between days 6 and 8 post-inoculation. Viral RNA was detectable in peripheral blood from day 2 post inoculation, until day 10 post inoculation. Severe gross lesions and histopathological changes were observed in lung, heart and stomach of infected animals.

Callaway (Nature 2020, see ***below***) provided a summary of the status of research on COVID-19 animal models in March 2020. He pointed to the preprint by Chao Shan at the Chinese Academy of Sciences Wuhan Institute of Virology, who found that rhesus macaques infected with SARS-CoV-2 had a fairly mild illness. The study followed 6 rhesus macaques over a period of 14 days after intratracheal inoculation with SARS-CoV-2, no changes in body temperature or weight loss were observed. No obvious clinical signs were observed except for mild anorexia in one animal. Blood, and oropharyngeal, nasal and anal swabs were collected over the course of the study; no viral RNA was detectable by RT-PCR in any of the blood samples, but was observed to peak in the oropharyngeal swabs on days 1 and 5 post inoculation, and was undetectable by day 9. Anal swabs tested positive in 3/6 animals on day 2, with one animal continuing to shed virus until day 11. Radiographs of their lungs showed signs of pneumonia similar to those in humans with COVID-19. Post-mortem examination showed gross pathology in the lower respiratory tract, including diffuse interstitial pneumonia. Two of the animals were observed for an extended period of three weeks; these monkeys lost some weight, but didn't seem to have other serious symptoms.

Munster (Nature 2020, see ***below***) also showed that SARS-CoV-2 causes respiratory disease in infected rhesus macaques, with disease lasting 8-16 days. Pulmonary infiltrates, a hallmark of human disease, were visible in lung radiographs. High viral loads were detected in swabs from the nose and throat of all animals as well as in bronchoalveolar lavages; in one animal we observed prolonged rectal shedding. Taken together, the rhesus macaque was found to recapitulate moderate disease observed in the majority of human cases.

Deng (Science 2020, see ***below***) studied the possibility of **reinfection** in a rhesus macaque model. Following the initial intratracheal infection, interstitial pneumonia and systemic viral dissemination mainly in the respiratory and gastrointestinal tracts were observed. Rhesus macaques reinfected with the identical SARS-CoV-2 strain during the early recovery phase of the initial SARS-CoV-2 infection did not show detectable viral dissemination, clinical manifestations of viral disease, or histopathological changes. Comparing the humoral and cellular immunity between primary infection and rechallenge revealed notably enhanced neutralizing antibody and immune responses (***Table 6***).

Protection against rechallenge in rhesus macaques has also been reported by Chandrashekar (Science 2020, see ***below***).

Yu (Animal Model Exp Med. 2020, see ***below***) found that SARS-CoV-2 caused more severe interstitial pneumonia in old monkeys than that in young monkeys. Monkeys developed typical interstitial pneumonia characterized by thickened alveolar septum accompanied with inflammation and oedema; notably, old monkeys exhibited diffuse severe interstitial pneumonia. Viral antigens were detected mainly in alveolar epithelial cells and macrophages.

Deng (Nature Comm 2020, see ***below***) also presented data suggesting that macaques can be infected with SARS-CoV-2 via the conjunctival route. Viral load and distribution in the macaques infected by this route were comparatively high in the nasolacrimal system, while relatively mild and local in the lung compared with those in macaques inoculated via intratracheal routes. This publication refers to the contrasting observation that no SARS-CoV-2 could be detected by RT-PCR in 114 conjunctival swabs samples 28 from patients with COVID-19 pneumonia.

Table 6 SARS-CoV-2 neutralizing antibody titers in infected monkeys (from Deng Science 2020)

Animal ID	Primary challenge		Re-challenge	
	21 dpi	28 dpi	33 dpi (5 dpr)	42 dpi (14 dpr)
M0[a]	n/a	n/a	n/a	n/a
M1[b]	n/a	n/a	n/a	n/a
M2	1:16	1:16	1:12	1:10
M3[c]	1:8	1:8	1:8	n/a
M4	1:16	1:16	1:40	1:160
M5[c]	1:20	1:16	1:32	n/a
M6	1:32	1:20	1:40	1:320

Notes: a M0 was euthanized and necropsied at 5 dpi.
b M1 was euthanized and necropsied at 7 dpi.
c M3 and M5 were euthanized and necropsied at 33 dpi (5 dpr).
n/a, not applicable.

African Green Monkeys

Totura (manuscript on Research Square: https://www.researchsquare.com/article/rs-21725/v1) experimentally inoculated 12 African Green or vervet monkeys (*Chlorocebus aethiops*) with aerosolised MERS-coronavirus and reported clinical signs similar to infected humans, with dose-dependent increases observed in respiratory disease signs and viral titres in serum and throat swabs of infected monkeys. The authors suggested that African green monkeys (AGM) may similarly provide a suitable animal model for COVID-19 studies. Woolsey (manuscript on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.05.17.100289v1.full) reported that AGM support a high level of SARS-CoV-2 replication and develop pronounced respiratory disease. SARS-CoV-2 was detected in mucosal samples and faeces of 6 AGM challenged with 5.0 x 10^5 PFU of the Italy isolate of SARS-CoV-2 (SARS-CoV-2/INMI1-Isolate/2020/Italy) by combined intratracheal and intranasal routes (dose divided equally) up to 15 days after virus exposure. Noteworthy is that virus replication and respiratory disease can be produced in AGM using a much lower and more natural dose of SARS-CoV-2 than has been employed in other non-human primate studies.

Further experimental infection of young AGM (N=6) revealed - through two imaging methods (18F-fluoro-2-deoxy-D-glucose positron emission tomography or 18F-FDG PET and computed tomography or CT) - pulmonary lesions at 4 days post-infection (dpi) that resolved over time. Infectious virus was shed from both respiratory and gastrointestinal tracts in all 6 animals in a biphasic manner, first between 2-7 dpi followed by a recrudescence at 14-21 dpi. All animals seroconverted simultaneously for IgM and IgG, which has also been documented in human COVID-19 cases (Hartman,

preprint on bioRxiv : https://doi.org/10.1101/2020.06.20.137687). The authors emphasize that young AGMs are suitable species to study mild/subclinical COVID-19 and are ideally suited for preclinical evaluation of candidate vaccines and therapeutic interventions.

Further data on the topic of reinfection were obtained from a longitudinal monitoring of nasopharyngeal swabs and serum of cohorts of AGM, one of which had been pre-exposed to SARS-CoV-2 (community-acquired exposure) prior to SARS-CoV-2 challenge. A dramatic increase from D1 to D18 in all diagnostic targets (RT-PCR, IgM and IgG) and neutralization (PRNT and microneutralization) across the entire NHP cohort was observed with the exception of the pre-infected animal. In this animal, a generally static level of neutralization was observed, IgG titers rose but interestingly IgM levels dropped over the course of the study (Ricks, manuscript on bioRxiv: https://doi.org/10.1101/2020.07.06.189803).

Surrogate models

Heegaard (Front Microbiol 2020, see ***below***) noted that the pig is an interesting case, as its ACE2 protein was both predicted and demonstrated experimentally to bind SARS-CoV-2 S protein; however, SARS-CoV-2 was found to neither replicate nor cause disease in pigs after experimental infection. Using a ten-fold higher viral dose for oronasal inoculation, Pickering (manuscript on bioRxiv : https://doi.org/10.1101/2020.09.10.288548) could detect evidence of infection, but only in a small proportion of animals. Heegaard suggested the use of a surrogate model based on intranasal inoculation of porcine respiratory coronavirus (PRCV) in pigs with robust metabolic syndrome such as obese Ossabaw miniature pigs, which may increase the severity of disease, similar to patients with metabolic syndrome having severe COVID-19.

Epidemiology

Disease emergence

On 31 December 2019, the Wuhan Municipal Health Commission announced a cluster of cases of viral pneumonia of unexplained aetiology (Wu Eurosurv 2020, see ***below***). The Southern China Seafood Wholesale Market in Wuhan was suspected to be related to 27 pneumonia cases without identified pathogenic agents that were reported in late December 2019. Most of the early cases were reportedly either shop owners, largely in the West District of the Southern China Seafood Wholesale Market, or people who visited the market before symptom onset. This market is a large open complex including sections selling seafood, fresh meat, produce, other perishable goods, and a very wide variety of live wild animals for consumption. Environmental disinfection of the Southern China Seafood Wholesale Market was initiated on 30 December 2019 and the market was closed on 1 January 2020.

Host range & search for intermediate animal hosts

In both the SARS-CoV and MERS-CoV epidemics, the viruses have likely originated from bats and then jumped into another amplification mammalian host [the Himalayan palm civet (*Paguma larvata*) for SARS-CoV and the dromedary camel (*Camelus dromedarius*) for MERS-CoV] before crossing species barriers to infect humans (Chan Em Micr Inf 2020, see ***below***). Bonilla-Aldana (manuscript on Preprints: https://www.preprints.org/manuscript/202003.0103/v2) performed a systematic literature review with meta-analysis, using three databases to assess MERS-CoV and SARS-CoV infection in animals and its diagnosis by serological and molecular tests to calculate pooled prevalence. From 34 studies (n=20,896 animals), the pool prevalence by RT-PCR for MERS-CoV was 7.2% (95%CI 5.6-8.7%), with 97.3% occurring in camels with a prevalence of 10.3% (95%CI 8.3-12.3). From 5 studies and 2,618 animals, for SARS-CoV, the RT-PCR pool prevalence was 2.3% (95%CI 1.3-3.3). Of those, 38.35% were reported on bats, in which the pool prevalence was 14.1% (95%CI0.0-44.6%). In this meta-analysis, camels and bats were found to be positive by RT-PCR in over 10% of the cases for both; thus, suggesting their relevance in the maintenance of wild zoonotic transmission.

While phylogenetic analysis indicates a bat origin of SARS-CoV-2, the virus also potentially recognizes the ACE2 receptor from a diversity of animal species (except mice and rats), implicating these animal species as possible intermediate hosts or animal models for SARS-CoV-2 infections (Wan, Shang, Granham et al. J Virol 2020, see ***below***). As explained by Andersen (Nature Med 2020, see ***below***), detailed understanding of how an animal virus jumped species boundaries to infect humans so productively will help in the prevention of future zoonotic events. If SARS-CoV-2 pre-adapted in another animal species, then there is the risk of future re-emergence events. In contrast, if the adaptive process occurred in humans, then even if repeated zoonotic transfers occur, they are unlikely to take off without the same series of mutations. Building on these gaps, the Wildlife Disease Surveillance Focus Group recommends the creation of a central, publicly accessible database for recording the characteristics of animal viruses to help monitor the risk of any crossover into people. This would allow scientists to see how the pathogens and their prevalence are evolving worldwide, helping them identify any potential vaccine targets or antiviral treatments before a major outbreak occurs (Gray Vet Record 2020, see ***below***).

Observations from genetic studies

A study by MacLean (bioRxiv 2020, see ***below***) revealed a low frequency of viral mutations among 15 537 SARS-CoV-2 genome sequences circulating in humans, suggesting that significant SARS-CoV-2 evolution occurred prior to spillover in humans. The authors warned that the high diversity of sarbecoviruses and their generalist nature make future emergence of divergent viral strains from bats to humans likely.

Ji (J Med Virol. 2020, see ***below***) suggested that snake is the most probable wildlife animal reservoir for SARS-CoV-2 based on its relative synonymous codon usage bias resembling snake compared to other animals. However, this hypothesis was received with skepticism (https://www.nature.com/articles/d41586-020-00180-8). It was not supported by the bioinformatics protein structure and sequence analyses by Zhang (manuscript on Arxiv: https://arxiv.org/abs/2002.03173). Lam (manuscript on bioRxiv : https://www.biorxiv.org/content/10.1101/2020.05.01.072371v6) modelled S-protein:ACE2 complexes from 215 vertebrate species, calculated their relative energies, correlated these energies to COVID-19 infection data, and analysed structural interactions. They predicted that known mutations are more detrimental in ACE2 than TMPRSS2, demonstrate phylogenetically that human SARS-CoV-2 strains originated from animal, and suggested that SARS-CoV-2 can infect a broad range of mammals, but not fish, birds or reptiles.

Chinese researchers of the South China Agricultural University in Guangzhou found 99% sequence similarity in the S RBD region between SARS-CoV-2 isolated from infected human subjects and coronaviruses taken from pangolins (*Manis javanica*) (https://www.nature.com/articles/d41586-020-00364-2). Researchers had noted previously that coronaviruses are a possible cause of death in pangolins, and that SARS-CoV-2 and coronaviruses from pangolins use receptors with similar molecular structures to infect cells. Lam (Nature 2020, see ***below***) also reported the identification of SARS-CoV-2-related coronaviruses in pangolins seized in anti-smuggling operations in southern China. Metagenomic sequencing identified pangolin-associated CoVs that belong to two sub-lineages of SARS-CoV-2-related coronaviruses, including one very closely related to SARS-CoV-2 in the RBD. Cyranoski (Nature 2020, see ***below***) subsequently summarized the investigations pertaining to the animal source of SARS-CoV-2. He noted that the previously communicated 99% homology between SARS-CoV-2 and a pangolin virus only applied to the S RBD region. The homology with pangolin viruses when considering the whole genome did not exceed 92.4%. A subsequent report by Zhang (Current Biology 2020, see ***below***) reached similar conclusions. By contrast, SARS-CoV shared 99.8% of its genome with a civet coronavirus.

Xiao (Nature 2020, see ***below***) reported the isolation of a coronavirus from a Malayan pangolin, which showed 100%, 98.6%, 97.8% and 90.7% amino acid identity with SARS-CoV-2 in the E, M, N and S genes, respectively. In particular, the receptor-binding domain within the S protein of the Pangolin-CoV is virtually identical to that of SARS-CoV-2, with one noncritical amino acid difference. Results of comparative genomic analysis suggested that SARS-CoV-2 might have

originated from the recombination of a Pangolin-CoV-like virus with a Bat-CoV-RaTG13-like virus. The Pangolin-CoV was detected in 17 of 25 Malayan pangolins analyzed. Infected pangolins showed clinical signs and histological changes, and circulating antibodies against Pangolin-CoV reacted with the S protein of SARS-CoV-2. The data suggest that pangolins have the potential to act as the intermediate host of SARS-CoV-2. Noteworthy is the evidence of Malayan pangolin SARS-CoV-2-related coronavirus (SARSr-CoV-2) is closely related to SARS-CoV-2 infecting multiple organs in pangolins, with the lungs being the major target, with ACE2 and TMPRSS2 co-expression with viral RNA. Importantly, viral RNA and protein were detected in 3 foetuses providing evidence for vertical virus transmission in pangolins (Li, preprint on bioRxiv: https://doi.org/10.1101/2020.06.22.164442).

Another prediction of the interaction between the RBD of the S protein and the ACE2 receptor surprisingly suggested that not only pangolins, but also turtles (*C. picta bellii*, *C. mydas*, and *P. sinensis*) might act as potential intermediate hosts transmitting SARS-CoV-2 to human (Liu, Xiao et al. J Med Vir 2020, see ***below***).

ACE2 contains at least five key amino acids critical for binding S protein of SARS-CoV-2. Based on these five amino acids, Luan (Biochem Biophys Res Commun 2020, see ***below***) analysed the corresponding amino acids of different mammals to determine which mammalian ACE2 could interact with the SARS-CoV-2 S protein. The authors found that the ACE2 of *Camelus dromedarius*, *Procyon lotor*, *Rhinolophus ferrumequinum*, *Rattus norvegicus*, *Mus musculus*, *Ornithorhynchus anatinus*, *Loxodonta africana*, *Erinaceus europaeus*, *Nyctereutes procyonoides*, *Suricata suricatta*, *Dipodomys ordii*, and *Cavia porcellus* are not able to associate with S protein. The authors indicated cat/dog ACE2 may bind to S protein of SARS-CoV-2. The ACE2 proteins from Circetidae, incl. *Mesocricetus auratus* (golden hamster) and *Cricetulus griseus* (Chinese hamster). Similarly, a study by Luan (J Med Vir 2020, see ***below***) also suggested that ACE2 proteins from Cricetidae were able to associate with SARS-CoV-2 RBD. The authors found a similar result for Bovidae. Rodrigues (manuscript on bioRxiv: https://doi.org/10.1101/2020.06.05.136861) investigated the structural properties of several ACE2 orthologs bound to the SARS-CoV-2 S protein and found that species not susceptible to SARS-CoV-2 infection have non-conservative mutations in several ACE2 amino acid residues which disrupt key polar and charged contacts with the viral spike protein. Their models predict affinity-enhancing mutations that could be used to design ACE2 variants for therapeutic purposes.

Robins (manuscript on bioRxiv: https://doi.org/10.1101/2020.06.05.136887) examined the protein covariance-based on the conserved CoV proteins called 1a/1b, S, 3a, E, M, and N from a set of 850 viral genome networks of SARS coronaviruses revealing interactions important to their emergence as human pathogens. They state that recombination with other viruses in combination with new adaptive mutations important for entry into human cells is the likely evolutionary scenario that converted a bat virus into human pathogen. Analysing ± 9,000 SARS-CoV-2 genomes from Africa, America, Asia, Europe, and Oceania, Jones (manuscript on bioRxiv: https://doi.org/10.1101/2020.06.05.135954) showed that the virus is a complex of slightly different genetic variants that are unevenly distributed on Earth, demonstrated that SARS-CoV-2 phylogeny is spatially structured and hypothesized this could be the result of founder effects occurring as a consequence of, and local evolution occurring after, long-distance dispersal.

Of note, while controversies about the source of the virus and its intermediate host remain, Li (Infect Genet Evol 2020, see ***below***) evaluated coronaviruses derived from five wild animals, including *Paguma larvata*, *Paradoxurus hermaphroditus*, Civet, *Aselliscus stoliczkanus* and *Rhinolophus sinicus* (Chinese rufous horseshoe bat). Genome and ORF1a homology analyses showed that SARS-CoV-2 is not the same coronavirus as the coronavirus derived from these five animals, whereas the authors confirmed the highest homology with Bat coronavirus isolate RaTG13. Latinne (Nature Comm 2020, see ***below***) next studied bat-CoVs (including 630 novel CoV sequences) macroevolution, cross-species transmission, and dispersal in China. Adopting a Bayesian approach the authors found inter-family and -genus switching is most common in Rhinolophidae bats and the genus *Rhinolophus* and present a phylogenetic analysis suggesting a likely origin for SARS-CoV-2 in *Rhinolophus* spp. bats. They further identify the host taxa and geographic

regions that define hotspots of CoV evolutionary diversity in China that could help target bat-CoV discovery for proactive zoonotic disease surveillance. Further bayesian evolutionary rate and divergence dates estimates were used to understand the role of reservoir species, the role of recombination and the time of SARS-CoV-2 divergence. As presented above (see ***Origin of the virus***), Boni (Nature 2020, see ***below***) showed that the sarbecoviruses—the viral subgenus containing SARS-CoV and SARS-CoV-2—undergo frequent recombination and exhibit spatially structured genetic diversity on a regional scale in China. SARS-CoV-2 itself is not a recombinant of any sarbecoviruses detected to date, and its receptor-binding motif, important for specificity to human ACE2 receptors, appears to be an ancestral trait shared with bat viruses and not one acquired recently via recombination. Boni and co-authors estimated that divergence time between SARS-CoV-2 and bat sarbecovirus reservoir were in 1948 (95% highest posterior density (HPD): 1879–1999), 1969 (95% HPD: 1930–2000) and 1982 (95% HPD: 1948–2009), indicating that the lineage giving rise to SARS-CoV-2 has been circulating unnoticed in bats for decades.

Susceptibility of various animal species to SARS-CoV-2

Field studies and laboratory challenge data remain important to conduct for better understanding the zoonotic transmission of SARS-CoV-2. One of these studies was conducted by Deng (Transbound Em Dis 2020, see ***below***), who after confirming the specificity, sensitivity and suitability of SARS-CoV-2 ELISA kit for different species of experimental animals, evaluated clinical serum samples from domestic livestock (pig, cow, sheep, horse), poultry (chicken, duck, goose), experimental animal (mice, rat, and rhesus monkey), companion animal (dog and cat), and wild animals (camel, fox, mink, alpaca, ferret, bamboo rat, peacock, eagle, tiger, rhinoceros, pangolin, leopard, cat, jackal, giant panda, masked civet, porcupine, bear, yellow-throated marten, weasel, red pandas, and wild boar). All serum samples had negative results, which made the authors conclude that the animal species above can be excluded as intermediate host of SARS-CoV-2. Of note, no SARS CoV-2 specific antibodies were detected in all dogs and cats, even for the street dogs and cats in Wuhan City and the pet dog raised by a COVID-19 patient.

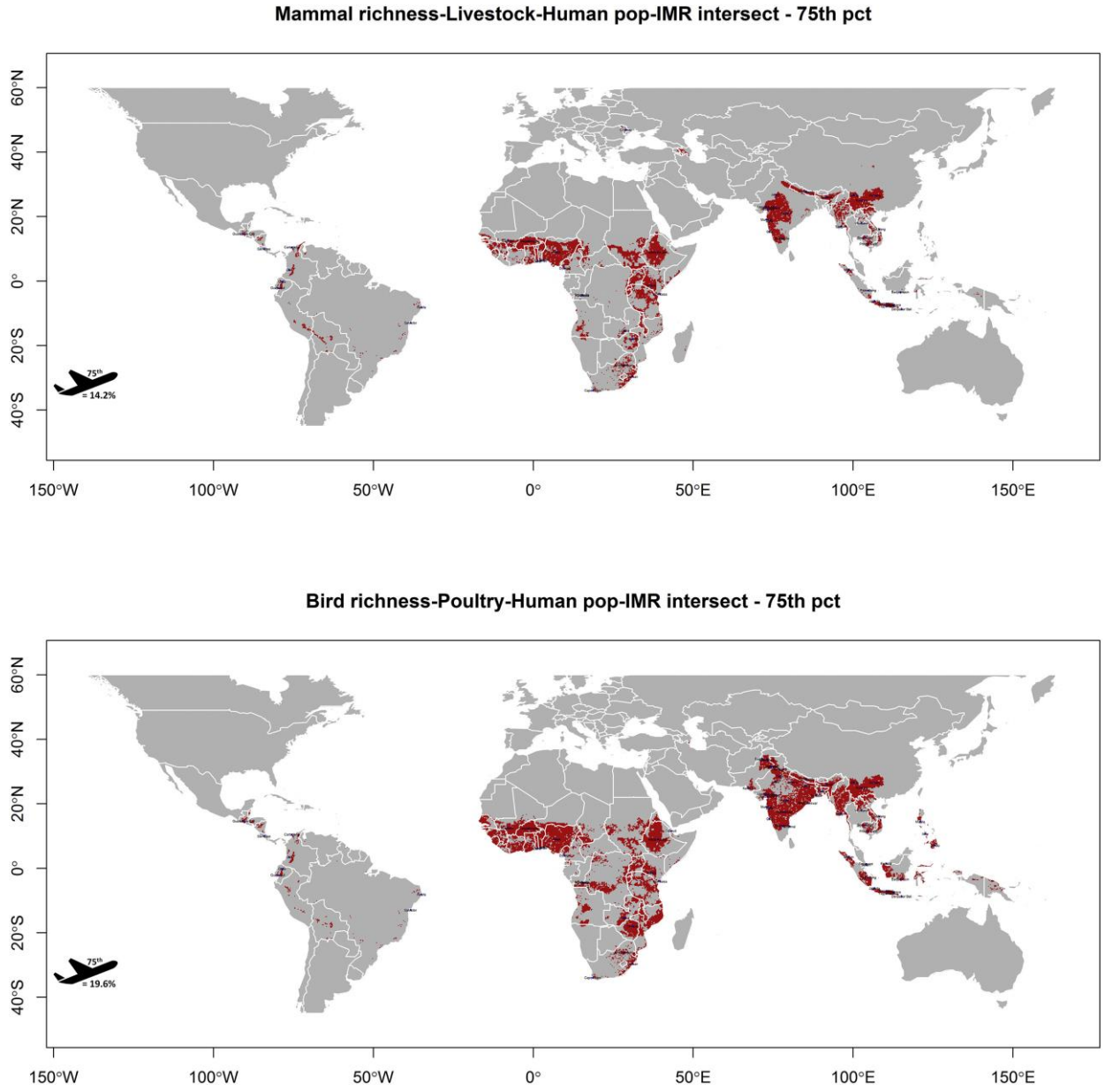
Rabbit (*Oryctolagus cuniculus*) and livestock (cattle, *Bos Taurus*) susceptibility to SARS-CoV-2 have been experimentally tested in more recent studies. While the infection is asymptomatic in healthy New Zealand White rabbits, infectious virus with peak titers corresponding to ~10^3 TCID50 could be detected up to day seven post inoculation in the nose. The minimum dose to establish productive infection was 10^5 TCID50, indicating that virus transmission between rabbits may be less efficient compared to ferrets and hamsters. The use of young, immunocompetent, and healthy rabbits however may not reflect virus shedding and disease in other rabbit breeds or rabbits at different ages. Thus, surveillance studies - including serological testing - may be needed to assess the presence of SARS-CoV-2 in farmed rabbits (Mykytyn preprint on bioRxiv : https://doi.org/10.1101/2020.08.27.263988). To examine the susceptibility of cattle for SARS-CoV-2 and to characterize the course of infection under experimental conditions, six 4-5 months old, male Holstein-Friesian dairy calves were intranasally inoculated with 1×10^5 tissue culture infectious dose 50% (TCID50) of SARS-CoV-2 strain "2019_nCoV Muc-IMB-1" (GISAID ID_EPI_ISL_406862, designation "hCoV-19/Germany/BavPat1/2020") at 1ml per nostril ; 24 hours after inoculation three contact cattle, were introduced. Ulrich (preprint on https://doi.org/10.1101/2020.08.25.254474) demonstrated that under selected experimental conditions cattle show low susceptibility to SARS-CoV-2, since two out of six animals appeared to be infected as demonstrated by SARS-CoV-2-genome detection in nasal swabs and specific seroconversion. The sample was small and - despite for controlling for bovine CoV cross-seroreactivity - results should be taken with caution.

SARS-CoV-2 emergence risk maps

A modelling study by Walsh (One Health 2020, see ***below***) provided a first systematic, data-driven, quantitative geography investigation of high-impact spillover wildlife-livestock/poultry-human interfaces taking into account human health system performance and global connectivity via the network of air travel. It showed that many of the world's most connected cities are adjacent to or within areas (50km radius) where wildlife share space with humans and their domesticated animals. Indeed, more than 40% of these cities were within or adjacent to landscapes of

extensive animal-human interface, while approximately 14%-20% were located in landscapes of both extensive interface and poor health system performance. The output is an alert-level map (yellow, orange, and red zones classified according to increased risk) which can be used as a tool to develop targeted surveillance systems and improving health infrastructure in vulnerable areas that may present conduits for future pandemics (***Figure 12***). As sensitive and SARS-Cov-2 specific tests (e.g. new ELISA) develop, and experimental evidence of transmission from infected animal hosts to naïve conspecifics and the nature and amount of viral shedding build up, new data should ultimately help refine the above-mentioned model and design more specific, data informed, SARS-CoV-2 emergence risk maps at fine scale human-animal interfaces.

Figure 12 Alert-level red zones depicting interfaces between mammalian richness, human population density, and livestock/ poultry densities based on the intersection of the top quartile of each feature's distribution, extending the intersection of these interfaces with the top quartile of infant mortality (from Walsh One Health 2020).



Cities of high network centrality (75th percentile) based on global air travel and within 50 km of red interfaces are overlaid. The proportion of highly connected transportation hubs (75th percentile of airport network centrality) within 50 km of each interface is presented with the airplane icon. Cities mapped twice have two high centrality airports.

Human to human transmission

Early observations

In the 99 patients cohort reported by Chen (Lancet 2020, see ***below***), 49 (49%) patients had a history of exposure to the Huanan seafood market, where wild animals were served at a restaurant. Among them, there were 47 patients with long-term exposure history, most of whom were salesmen or market managers, and two patients with short-term exposure history, who were shoppers. None of the patients were medical staff. These early data suggested that a point-source zoonotic (animal-to-human) route was likely the main mode of transmission of the disease (Nishiura J Clin Med 2020, see ***below***). However, the reporting of a family cluster including a family member, who did not travel to Wuhan, but became infected with the virus after several days of contact with four of the family members, soon provided strong evidence of human-to-human transmission (Chan Lancet 2020, see ***below***). In this cluster none of the family members had contacts with Wuhan markets or animals, although two had visited a Wuhan hospital. In line with this observation, the genetic epidemiology data suggest that from the beginning of December, 2019, when the first cases were retrospectively traced in Wuhan, the spread of infection has been almost entirely driven by human-to-human transmission, not the result of continued spillover (Heymann Lancet 2020, see ***below***).

Transmission mode

In March 2020, Han (Infl Other Resp Inf 2020, see ***below***) summarized available information on the different transmission modes of SARS-CoV-2. A more recent review has been provided by Kutti-Sridharan (Int J Prev Med 2020, see ***below***). It appears that SARS-CoV-2 has the potential to be spread by all modes of transmission: direct contact (i.e., person-to-person) and indirect contact (e.g., via contaminated objects and aerosol) (Fennelly Lancet Resp Med 2020, see ***below***; Santarpia Sci Rep 2020, see ***below***; and for instance, Cai Em Inf Dis 2020, see ***below***). As of today, it is not yet clear which mode occurs most frequently.

Respiratory secretions and saliva

Virus shedding has been demonstrated in multiple studies that analysed respiratory secretions by RT-PCR testing (see for instance Zou NEJM 2020 ***below***; more detailed data on virus shedding are presented in section ***Virus shedding & virus load*** above).

The duration of shedding was initially measured by RT-PCR and found highly variable (see ***Kinetic studies***). A study by Zhou (Clin Inf Dis, see ***below***), for instance, reported virus detection in throat samples for a median duration of 31.0 (IQR: 24.0-40.0) days from illness onset, ranging between 18 and 48 days. A review by Fontana (Inf Contr Hosp Epi 2020, see ***below***) found an overall pooled median duration of RNA shedding from respiratory sources of 18.4 days (95% CI: 15.5 days - 21.3 days; I2=98.87%, p<0.01) among 28 studies. Viable virus was isolated by culture from -6 days to 20 days relative to symptom onset. Importantly, limited correlation was found between SARS-CoV-2 detection by RT-PCR and presence of culturable virus.

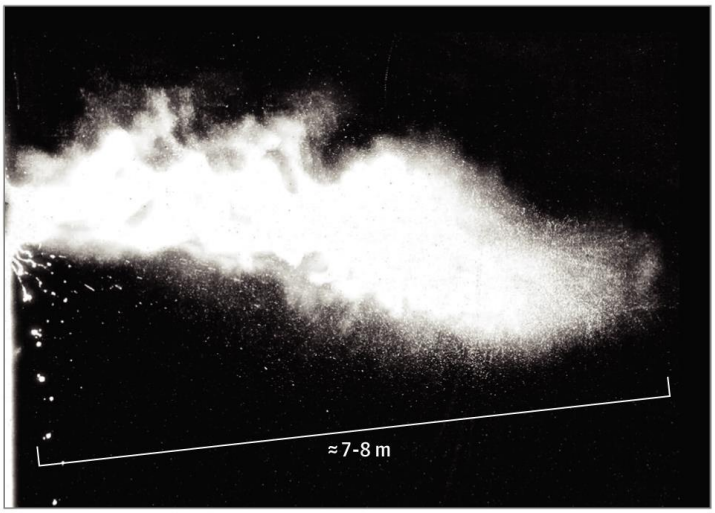
Respiratory droplet emissions are typically dichotomized into “large” and “small” droplets. Large droplets settle faster than they evaporate, contaminating the immediate vicinity of the infected individual. In contrast, small droplets evaporate faster than they settle (Bourouiba JAMA 2020, see ***below***). In this model, as small droplets transition from the warm and moist conditions of the respiratory system to the colder and drier outside environment, they evaporate and form residual particulates made of the dried material from the original droplets. These residual particulates are referred to as aerosols. Such classification systems employ various arbitrary droplet diameter cutoffs, from 5 to 10 µm, to categorize host-to-host transmission as droplets or aerosol routes.

However, more recent work has demonstrated that exhalations, sneezes, and coughs not only consist of mucosalivary droplets following short-range semi-ballistic emission trajectories but are primarily made of a multiphase turbulent gas cloud that entrains ambient air and traps and carries within it clusters of droplets with a continuum of droplet

sizes. The locally moist and warm atmosphere within the turbulent gas cloud allows the contained droplets to evade evaporation for much longer than occurs with isolated droplets. Under these conditions, the lifetime of a droplet could be considerably extended by a factor of up to 1000, from a fraction of a second to minutes. Given various combinations of an individual patient's physiology and environmental conditions, such as humidity and temperature, the gas cloud and its payload of pathogen-bearing droplets of all sizes can travel 23 to 27 feet (7-8 m) (***Figure 13***). Although no studies have directly evaluated the biophysics of droplets and gas cloud formation for patients infected with SARS-CoV-2, several properties of the exhaled gas cloud and respiratory transmission may apply to this pathogen.

Stadnytskyi (PNAS 2020, see ***below***) reported data suggesting a substantial probability that normal speaking causes airborne virus transmission in confined environments. Highly sensitive laser light scattering observations revealed indeed that loud speech can emit thousands of oral fluid droplets per second. In a closed, stagnant air environment, they disappear from the window of view with time constants in the range of 8 to 14 min, which corresponds to droplet nuclei of ca. 4 µm diameter, or 12- to 21-µm droplets prior to dehydration.

Figure 13 Multiphase Turbulent Gas Cloud From a Human Sneeze (from Bourouiba JAMA 2020)



In July 2020, a commentary signed by 239 scientists appealed to the medical community and to the relevant national and international bodies to recognize the potential for airborne spread of COVID-19 (Morawska Clin Infect Dis 2020, see ***below***). The authors indicated that there is significant potential for inhalation exposure to viruses in microscopic respiratory droplets (microdroplets) at short to medium distances (up to several meters, or room scale), and advocated for the use of preventive measures to mitigate this route of airborne transmission. A viewpoint published at the same time by Klompas (JAMA 2020, see ***below***), also provided a strong rationale to support the importance of this route of transmission.

More recently, a short letter by Prather (Science 2020, see ***below***) pointed to the need to harmonize discussions about modes of virus transmission across disciplines to ensure the most effective control strategies and provide clear and consistent guidance to the public. The authors confirmed the need to distinguish between aerosols and droplets using a size threshold of 100 µm, instead of the historical 5 µm, as this size more effectively separates their aerodynamic behaviour, ability to be inhaled, and efficacy of interventions. Viruses in droplets (larger than 100 µm) typically fall to the ground in seconds within 2 m of the source. Because of their limited travel range, physical distancing reduces exposure to these droplets. Viruses in aerosols (smaller than 100 µm) can remain suspended in the air for many seconds to hours and be inhaled. They are highly concentrated near an infected person, so they can infect people most easily in close proximity. But aerosols containing infectious virus can also travel more than 2 m and accumulate in poorly ventilated indoor air, leading to superspreading events.

Some recent reports indicate that individuals with COVID-19, many of whom have no symptoms, release thousands of virus-laden aerosols and far fewer droplets when breathing and talking. These data led Prather to consider that one is far more likely to inhale aerosols than be sprayed by a droplet. In addition to existing mandates of mask-wearing, social distancing, and hygiene efforts, the authors urged public health officials to add clear guidance about the importance of moving activities outdoors, improving indoor air using ventilation and filtration, and improving protection for high-risk workers

Conjunctiva

Two samples of tear and conjunctival secretions obtained from a COVID-19 patient with conjunctivitis yielded positive RT-PCR results (Xia J Med Vir 2020, see ***below***). A manuscript by Sun (on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.26.20027938v1) reported a similar observation, with SARS-COV-2 RNA detected in ocular discharges in one patient with conjunctivitis. Although conjunctivis is a rare symptom of COVID-19 (observed in 2.8% of patients in this study), the authors suggested a potential route of nosocomial infection through the eyes after occupational exposure. Furthermore, Colavita (Ann Intern Med. 2020, see ***below***) demonstrated that ocular fluids from SARS-CoV-2-infected patients may contain **infectious virus**. The first RNA-positive ocular sample of a 65-year-old woman, who had travelled from Wuhan to Italy, was inoculated in Vero E6 cells, and cytopathic effect was observed 5 days postinoculum. Viral replication was confirmed by real-time RT-PCR on RNA purified from spent cell growth medium.

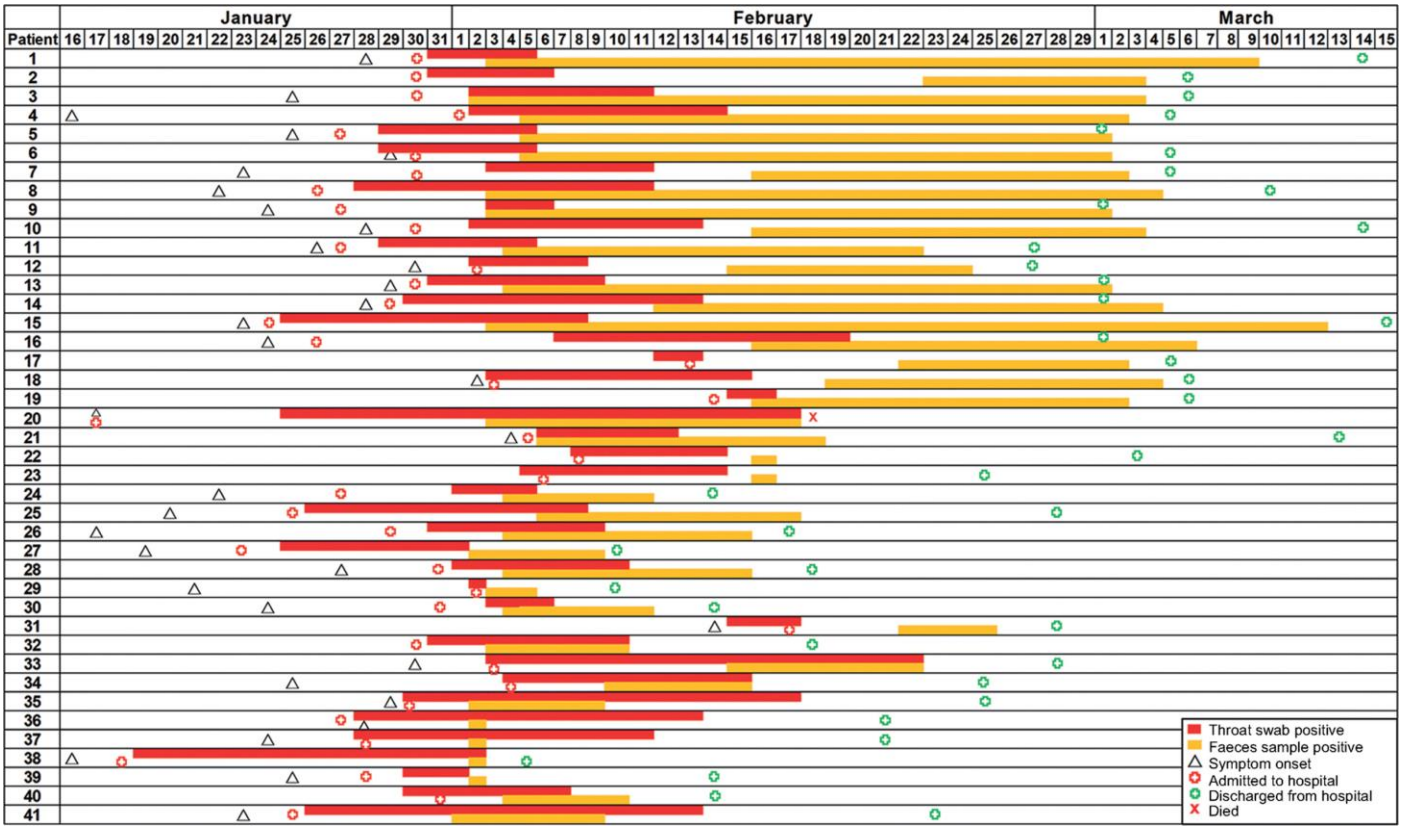
Peng (J Med Vir 2020, see ***below***) suggested that the detection of SARS-CoV-2 RNA in tears and conjunctival secretions of very few COVID-19 patients complicated with conjunctivitis is a coincident event, rather than a causal event of SARS-CoV-2 infection of the conjunctiva. Similarly, Seah (Ophtalmology 2020, see ***below***) evaluated virus shedding in tears in 17 COVID-19 patients. All tear samples showed negative results, even when nasopharyngeal swab samples continued to show positive results. Furthermore, patients with symptoms of upper respiratory tract infections did not demonstrate any viral shedding in tears, suggesting that the hypothesis of the lacrimal duct as a viral conduit may not be true. Most importantly, only 1 patient showed ocular symptoms during the disease course, and no evidence of SARS-CoV-2 could be found in the tear samples. This suggests that transmission through tears regardless of the phase of infection likely is low.

Faecal excretion

The observation that 14 out of 138 patients (10 percent) in a Wuhan hospital (Wang JAMA 2020, see ***below***) initially presented with diarrhoea and nausea one or two days prior to development of fever and dyspnoea supported the hypothesis of faecal transmission of the virus. A similar observation had already been made with the first U.S. patient diagnosed with COVID-19, who also experienced loose bowel movements for two days and subsequent viral RNA detection in stool. Zhang (Emerg Micr Inf 2020, see ***below***) reported presence of virus RNA in anal swabs and blood, with more anal swab positives than oral swab positives in a later stage of infection. Xiao (Gastroent 2020, see ***below***) found 53.42% of patients testing positive in stool. 23.29% of the patients remained positive in faeces even after the viral RNA decreased to undetectable level in respiratory tract.

Wu (Lancet Gastroenterol Hepatol 2020, see ***below***) presented real-time RT-PCR results of respiratory and faecal samples from COVID-19 patients. Faecal samples from 33 (45%) of 74 patients were negative for SARS CoV-2 RNA, while their respiratory swabs remained positive for a mean of 15·4 days (SD 6.7) from first symptom onset. Of the 41 (55%) of 74 patients with faecal samples that were positive for SARS-CoV-2 RNA, respiratory samples remained positive for SARS-CoV-2 RNA for a mean of 16·7 days (SD 6.7) and faecal samples remained positive for a mean of 27·9 days (10.7) after first symptom onset. The full disease course of the 41 patients with faecal samples that were positive for SARS-CoV-2 RNA is shown in ***Figure 14***. Notably, patient 1 had positive faecal samples for 33 days continuously after the respiratory samples became negative, and patient 4 tested positive for SARS-CoV-2 RNA in their faecal sample up to 47 days after first symptom onset.

Figure 14 Timeline of results from throat swabs and faecal samples through the course of disease for patients with SARS-CoV-2 RNA positive faecal samples (from Wu Lancet Gastroenterol Hepatol. 2020)



Similarly, from a cohort of 42 patients, Chen, Chen et al. (J Med Vir 2020, see ***below***) identified 18 (64.29%) patients who remained positive for viral RNA in faeces after pharyngeal swabs turned negative. Viral shedding in faeces continued for 7 (6-10) days after pharyngeal swabs became negative, regardless of COVID-19 severity.

In a meta-analysis of 60 studies, comprising 4243 COVID-19 patients, the pooled prevalence of all gastrointestinal symptoms was 17.6% (95% CI, 12.3%-24.5%); 11.8% of patients with non-severe COVID-19 had gastrointestinal symptoms (95% CI, 4.1%-29.1%) and 17.1% of patients with severe COVID-19 had gastrointestinal symptoms (95% CI, 6.9%-36.7%) (Cheung Gastroenterol 2020, see ***below***). The pooled prevalence of stool samples that were positive for virus RNA was 48.1% (95% CI, 38.3%-57.9%); of these samples, 70.3% of those collected after loss of virus from respiratory specimens tested positive for the virus (95% CI, 49.6%-85.1%).

Vertical transmission

Preliminary studies soon suggested the absence of vertical transmission of SARS-CoV-2 (see for instance Chen Lancet 2020, see ***below***). Subsequent reports largely supported this contention, even though the possibility that vertical transmission might occur in some cases could not be completely ruled out (see ***Pregnancy and newborns*** above). A very recent review of available data by Bwire (J Med Vir 2020, see ***below***) concluded that the current evidence reveals a low possibility of vertical transmission of COVID-19.

Blood products

SARS-CoV-2 shedding in plasma or serum is common, which leads to a theoretical risk of transmission of coronaviruses through transfusion of blood products. Chang (Transfus Med Rev 2020, see ***below***) noted that because more and more asymptomatic infections are being found among COVID-19 cases, considerations of blood safety and coronaviruses have arisen especially in endemic areas.

Semen

A study by Song (Biol Reprod 2020, see ***below***) analysed semen samples collected from 12 patients in their recovery phase, as well as in testicular samples from one patient who died of COVID-19 during the acute phase. All samples were negative by RT-PCR, suggesting that SASR-CoV-2 does not infect the testis and the male reproductive tract.

Ruling out vector-borne transmission

The possibility of vector borne transmission of SARS-CoV-2 has been debated since the beginning of the COVID-19 pandemic. Huang (Sci Rep 2020, see ***below***) tested experimentally the capacity of SARS-CoV-2 to infect and be transmitted by three widely distributed species of mosquito (*Aedes aegypti*, *Ae. albopictus* and *Culex quinquefasciatus*). They carried out intrathoracic inoculation of mosquitoes with SARS-CoV-2 WA1/2020 strain. Based upon the lack of detectable infectious virus in any of the 277 samples collected at all time points beyond 24 h post-inoculation, they concluded that SARS-CoV-2 is unable to replicate in mosquitoes and therefore cannot be transmitted to people in that way. Only 3 species were tested and one cannot arbitrarily rule out susceptibility of all human-biting mosquitoes in localities where infected people are found. However, the results of Huang and colleagues strongly suggest that mosquitoes in general are not susceptible to infection by this virus, which should end speculation about biological transmission of SARS-CoV-2 by mosquitoes being epidemiologically significant. Mechanical transmission (soiled mouth parts) by interrupted mosquito feeding would require very high viremias in infected individuals (probably 10^{6-7} or more and for which there is no evidence) followed almost immediately by feeding on a susceptible person (Promed archive number : 20200721.7595820). Xia (Virol Sinica 2020, see ***below***) performed experimental infection of wild mosquitoes (Aedes cells C6/36 and Aag2 in vitro) collected in Wuhan. They also showed that SARS-CoV-2 does not replicate in the field collected Culex and Anopheles mosquitoes, supporting the lack of evidence for mosquito-borne transmission of SARS-CoV-2. The susceptibility of biting insects to SARS-CoV-2 has been further examined after experimental feeding on SARS-CoV-2 infected blood meal (Balaraman, manuscript on bioRxiv : https://doi.org/10.1101/2020.09.29.317289). Species tested included *Culicoides sonorensis* biting midges, *Culex tarsalis* and *Culex quinquefasciatus* mosquitoes, all known biological vectors for numerous RNA viruses. Arthropods were allowed to feed on SARS-CoV-2 spiked blood and at various time points post-infection analysed for the presence of viral RNA and infectious virus. Additionally, cell lines derived from *C. sonorensis* (W8a), *Ae. aegypti* (C6/36), *Cx. quinquefasciatus* (HSU), and *Cx. tarsalis* (CxTrR2) were tested for SARS-CoV-2 susceptibility. Their results indicated that none of the biting insects, nor the insect cell lines support SARS-CoV-2 replication and, similar to previous studies, concluded that biting insect do not pose a risk for transmission of SARS-CoV-2 to humans or animals following an infected blood meal.

Social drivers of transmission

While the basic reproductive number only captures the average dynamics of transmission, a crucial question for control is whether specific situations and settings might be driving the epidemic (Liu Lancet 2020, see ***below***). The secondary attack rate, defined as the probability that an infection occurs among susceptible people within a specific group (i.e., household or close contacts), can provide an indication of how social interactions relate to transmission risk. Drawing on data from nine recent reports of secondary transmission associated with a specific event such as a meal or holiday visit, Liu estimated that 48 secondary infections occurred among 137 attendees. Assuming that all these secondary infections were generated by a single primary case, which is probable given the short-term nature of the exposure events, would imply a secondary attack rate among close contacts of 35% (95% CI 27-44). More data are needed to reliably estimate the true within-household and between-household transmission for SARS-CoV-2; recent reports might be biased towards larger transmission events. However, if it transpires that most at-risk contacts have a close relationship with cases, and superspreading events tend to occur at large gatherings of these close contacts measures to reduce infection risk during such gatherings and subsequent tracing of close contacts of cases might have a disproportionate effect on reducing overall transmission.

Public transportation

A retrospective analysis of early data found a significant association between domestic travel by train and the number of COVID-19 cases in China, whereas the associations of the other two means of transportation (car, flight) failed to reach statistical significance (Zhao Travel Med Inf Dis 2020, see ***below***). However, a subsequent analysis by Chen (Chin Med J 2020, see ***below***), based on cases up to Jan 30 and population migration data extracted from Baidu Qianxi, found a correlation coefficient between the provincial number of cases and emigration from Wuhan up to 0.943.

Zheng (Trav Med Inf Dis 2020, see ***below***) studied the spatial transmission of COVID-19 via public and private transportation in China, and found a significant and positive association between the frequency of flights, trains, and buses from Wuhan and the daily as well as the cumulative numbers of COVID-19 cases in other cities with progressively increased correlations for trains and buses.

A study by Lau (J Microbiol Immunol Infect 2020, see ***below***) indicated that the number of flight routes as well as total passenger volume are highly relevant risk factors for the spread of current COVID-19.

Qifang Bi on medRxiv (https://www.medrxiv.org/content/10.1101/2020.03.03.20028423v1) studied 391 cases and 1286 close contacts identified by the Shenzhen CDC. In this dataset, cases were found older than the general population (mean age 45) and balanced between males (187) and females (204). Household contacts and those travelling with a case where at higher risk of infection (ORs 6 and 7) than other close contacts.

A rapid review by Zhen (S Afr Med J 2020, see ***below***) also suggested an increased risk of viral transmission with public transportation use, which may be reduced with improved ventilation.

Mass gatherings

Ebrahim (Trav Med Inf Dis 2020, see ***below***) highlighted the fact that mass gatherings, both those clearly defined and those spontaneously occurring, are key determinants of epidemiologic expansion of disease outbreaks. The authors noted that COVID-19 had already provided examples of both clearly planned event cancellations such as the Umrah suspension in Saudi Arabia, and situations where outbreaks and events were continued.

Schools

To what extent schools and kindergartens impact SARS-CoV-2 transmission remains a topic of debate. Studies to determine the contribution of children as sources of infection are complicated by the fact that non-pharmaceutical interventions including school- and kindergarten closures were in place before observational trials could begin. A household study in China and observations in a limited number of contact investigations in Germany suggest that children are infected by SARS-CoV-2 at a rate that may not be different from that of adults. However, the extent to which children can act as sources of infection remains unclear (Jones, manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.06.08.20125484v1).

Estimates of key epidemiological parameters

Serial interval

The serial interval of COVID-19 is defined as the time duration between a primary case (infector) developing symptoms and secondary case (infectee) developing symptoms (Du Em Inf Dis 2020, see ***below***). Obtaining robust estimates for the distribution of COVID-19 serial intervals is a critical input for determining the reproduction number which can indicate the extent of interventions required to control an epidemic. The serial intervals reported by Du had a mean of 3.96 days (95% confidence interval: 3.53-4.39), a standard deviation of 4.75 days (95% confidence interval: 4.46-5.07), and 12.6% of reports indicating pre-symptomatic transmission.

Subsequently, from the analysis of a total of 28 infector-infectee pairs, Nishiura (Int J Inf Dis 2020, see ***below***) estimated the median serial interval at 4.0 days (95% credible interval [CrI]: 3.1, 4.9). Limiting our data to only the

most certain pairs, the median serial interval was estimated at 4.6 days (95% CrI: 3.5, 5.9). Considering that the serial interval of COVID-19 is close to or shorter than its median incubation period, the data suggest that a substantial proportion of secondary transmission may occur prior to illness onset.

Zhao (Infect Control Hosp Epidemiol. 2020, see ***below***) evaluated 48 transmission events including 21 in Hong Kong and 27 in Shenzhen. The authors found find that the serial interval had been decreasing by 0.4 (95%CI: 0.1−0.7) per day, or 6.2% (95%CI: 0.4−11.6%) in percentage, from January 10 to February 2 in Hong Kong and Shenzhen. The Pearson correlation coefficient between the serial interval and calendar date was estimated at −0.37 with p-value < 0.01. The serial interval of male primary cases was 3.5 days (95%CI: 1.2−5.7) shorter than that of a female primary case, or 49.7% (95%CI: 15.3−70.1%) less in percentage.

The systematic review of COVID-19 epidemiology by Park (J Clin Med 2020, see ***below***), which included 41 studies, estimated the serial interval to be 4-8 days.

Reproductive number

Different estimates of the basic reproductive number (R_0) were reported from a number of studies since the start of the epidemic (see ***Table 7***).

A preliminary R_0 estimate of 1.4-2.5 was presented at the "meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)" (https://www.who.int/news-room/detail/23-01-2020-statement-on-the-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov))

Liu (J Trav Med 2020, see ***below***) had previously presented an overview of published R_0 estimates for the disease, and found the average R_0 to be 3.28 and median 2.79.

Zhao (J Trav Med 2020, see ***below***) subsequently demonstrated that using an overestimated serial interval leads to overestimation of R_0, and found an R_0 at 2.0 when using a more recent estimate of the serial interval at 4.6 days.

Table 7 Published estimates of R_0 (adapted from Liu J Trav Med 2020)

Study	Location	Study date	Methods	Approaches	R_0 estimates (average)	95% CI
WHO	China	18 January 2020	/	/	1.4–2.5 (1.95)	/
Joseph	Wuhan	31 December 2019–28 January 2020	Stochastic Markov Chain Monte Carlo methods (MCMC)	MCMC methods with Gibbs sampling and non-informative flat prior, using posterior distribution	2.68	2.47–2.86
Shen	Hubei province	12–22 January 2020	Mathematical model, dynamic compartmental model with population divided into five compartments: susceptible individuals, asymptomatic individuals during the incubation period, infectious individuals with symptoms, isolated individuals with treatment and recovered individuals	R0 = β/αβ = mean person-to-person transmission rate/day in the absence of control interventions, using nonlinear least squares method to get its point estimateα = isolation rate = 6	6.49	6.31–6.66
Liu	China and overseas	23 January 2020	Statistical exponential Growth, using SARS generation time = 8.4 days, SD = 3.8 days	Applies Poisson regression to fit the exponential growth rateR0 = 1/M(−r)M = moment generating function of the generation time	2.90	2.32–3.63

Study	Location	Study date	Methods	Approaches	R_0 estimates (average)	95% CI
				distributionr = fitted exponential growth rate		
Liu	China and overseas	23 January 2020	Statistical maximum likelihood estimation, using SARS generation time = 8.4 days, SD = 3.8 days	Maximize log-likelihood to estimate R0 by using surveillance data during a disease epidemic, and assuming the secondary case is Poisson distribution with expected value R0	2.92	2.28–3.67
Read	China	1–22 January 2020	Mathematical transmission model assuming latent period = 4 days and near to the incubation period	Assumes daily time increments with Poisson-distribution and apply a deterministic SEIR metapopulation transmission model, transmission rate = 1.94, infectious period =1.61 days	3.11	2.39–4.13
Majumder	Wuhan	8 December 2019 and 26 January 2020	Mathematical Incidence Decay and Exponential Adjustment (IDEA) model	Adopted mean serial interval lengths from SARS and MERS ranging from 6 to 10 days to fit the IDEA model,	2.0–3.1 (2.55)	/
Cao	China	23 January 2020	Mathematical model including compartments Susceptible-Exposed-Infectious-Recovered-Death-Cumulative (SEIRDC)	R = K 2 (L × D) + K(L + D) + 1L = average latent period = 7,D = average latent infectious period = 9,K = logarithmic growth rate of the case counts	4.08	/
Zhao	China	10–24 January 2020	Statistical exponential growth model method adopting serial interval from SARS (mean = 8.4 days, SD = 3.8 days) and MERS (mean = 7.6 days, SD = 3.4 days)	Corresponding to 8-fold increase in the reporting rateR0 = 1/M(−r)r =intrinsic growth rateM = moment generating function	2.24	1.96–2.55
Zhao	China	10–24 January 2020	Statistical exponential growth model method adopting serial interval from SARS (mean = 8.4 days, SD = 3.8 days) and MERS (mean = 7.6 days, SD = 3.4 days)	Corresponding to 2-fold increase in the reporting rateR0 = 1/M(−r)r =intrinsic growth rateM = moment generating function	3.58	2.89–4.39
Imai	Wuhan	18 January 2020	Mathematical model, computational modelling of potential epidemic trajectories	Assume SARS-like levels of case-to-case variability in the numbers of secondary cases and a SARS-like generation time with 8.4 days, and set number of cases caused by zoonotic exposure and assumed total number of cases to estimate R0 values for best-case, median and worst-case	1.5–3.5 (2.5)	/
Julien and Althaus	China and overseas	18 January 2020	Stochastic simulations of early outbreak trajectories	Stochastic simulations of early outbreak trajectories were performed that are consistent with the epidemiological findings to date	2.2	
Tang	China	22 January 2020	Mathematical SEIR-type epidemiological model incorporates appropriate compartments corresponding to interventions	Method-based method and Likelihood-based method	6.47	5.71–7.23
Qun Li	China	22 January 2020	Statistical exponential growth model	Mean incubation period = 5.2 days, mean serial interval = 7.5 days	2.2	1.4–3.9
Lai[4]					2.6 (range 2.1-5.1)	

[4] J Med Vir 2020

Study	Location	Study date	Methods	Approaches	R_0 estimates (average)	95% CI
Sanche[5]					4.7 - 6.6	2.8 - 11.3
Li[6]					2.2	1.4-3.9
Zhao[7]					2.24	1.96-2.55
Zhao					3.58	2.89-4.39
Riou[8]					median 2.2	90% high density interval: 1.4–3.8
Zhou[9]					2.8 - 3.3 or 3.2 - 3.9	
Wu[10]					2·68	2·47-2·86
Liu[11]					3.28	
Shao[12]	China				3.25≤ R_0 ≤3.4	
Sanche[13]					median 5.7	3.8–8.9
D'Arienzo[14]	Italy	25 February – 12 March 2020	Mathematical SIR model		2.43 - 3.10	

The systematic review of COVID-19 epidemiology by Park (J Clin Med 2020, see ***below***), which included 21 estimates for the basic reproduction number ranging from 1.9 to 6.5, noted that 13/21 estimates were found between 2.0 and 3.0.

The effective reproduction number (R, the expected number of secondary cases generated by an infectious case once the epidemic is underway) is now assessed by a growing number of studies, and the impact of public health interventions thereby illustrated (see ***Modelling the impact of public health measures*** below).

Liu (on medRxiv: https://www.biorxiv.org/content/10.1101/2020.01.25.919787v2) reported a continuous decline in the R values especially after January 16 nationwide and in Wuhan. Such temporal effect was also observed by Kucharski (Lancet Inf Dis 2020, see ***below***), who estimated that the median daily reproduction number (Rt) in Wuhan declined from 2.35 (95% CI 1.15–4.77) 1 week before travel restrictions were introduced on Jan 23, 2020, to 1.05 (0.41–2.39) 1 week after. Interestingly, Kucharski's model also found that in locations with similar transmission potential to Wuhan in early January, once there are at least four independently introduced cases, there is a more than 50% chance the infection will establish within that population.

[5] Em Inf Dis 2020
[6] NEJM 2020
[7] Int J Infect Dis 2020
[8] Eurosurv 2020
[9] J Evid Based Med 2020
[10] Lancet 2020
[11] J Travel Med 2020
[12] https://www.medrxiv.org/content/10.1101/2020.02.17.20023747v2
[13] Emerg Infect Dis 2020
[14] Biosaf Health. 2020

In another example, Salje (Science 2020, see ***below***) estimated that in France, the lockdown reduced the reproductive number of the disease from 2.90 to 0.67. By 11 May 2020, when interventions were scheduled to be eased, the authors projected 2.8 million (range: 1.8-4.7) people, or 4.4% (range: 2.8-7.2) of the population, would have been infected.

Attack rate of the disease

Information is still lacking as to the incidence of the disease in various populations. However, some publications have assessed the disease prevalence in specific cohorts of subjects.

A study by Wang (Trav Med Inf Dis 2020, see ***below***) estimated the prevalence of COVID-19 in 2004 participants under home quarantine in Shenzhen. Of people who provided clear travel history, 129 people have travelled to Wuhan city and 1,046 people have travelled to other cities in Hubei province within 14 days before the home quarantine. Few (less than 1%) participants reported contact history with confirmed or suspected cases during their trip and most arrived in Shenzhen more than a week before the study. Three cases were found in the cohort, corresponding to 1.5‰ prevalence (95% CI: 0.31‰-4.37‰).

Contact tracing of 2,370 individuals from the first 30 COVID-19 cases in Korea indicated that the risk of symptomatic cases from transmission to contacts was low at 0.55% (95% CI 0.31–0.96) (COVID-19 National Emergency Response Center Osong Public Health Res Perspect 2020, see ***below***). However, the findings also suggested that the transmission of COVID-19 was significant among household contacts: there were 119 household contacts, of which 9 individuals developed COVID-19 resulting in a secondary attack rate of 7.56% (95% CI 3.7–14.26), which is in line with other reports. In the earlier reports, familial clusters of COVID-19 had been reported and household transmission was thought to be a major driver in the spread of the outbreak in the community. Of the first 262 COVID-19 cases in Beijing, China, 133 (50.8%) were family cluster cases. In the US, active symptom monitoring was performed for 445 close contacts of the 12 cases with travel-related COVID-19, resulting in symptomatic cases with a secondary attack rate of 0.45% (95% CI, 0.12–1.6) among all contacts, and 10.5% (95% CI, 2.9–31.4) among household members.

Li (Clin Inf Dis 2020, see ***below***) enrolled 105 index patients and 392 household contacts to determine the features of household transmission of COVID-19. Secondary transmission of SARS-CoV-2 developed in 64 of 392 household contacts (16.3%). The secondary attack rate to children was 4% comparing with 17.1% to adults. The secondary attack rate to the contacts within the households with index patients quarantined by themselves since onset of symptoms was 0% comparing with 16.9% to the contacts without index patients quarantined. The secondary attack rate to contacts who were spouses of index cases was 27.8% comparing with 17.3% to other adult members in the households.

Lytras (J Travel Med 2020, see ***below***) reported screening data from passengers on repatriation flights to Greece from the UK, Spain and Turkey. Despite almost all passengers being asymptomatic, many tested positive (3.6% from UK, 6.3% from Spain and 6.3% from Turkey).

Dispersion factor and superspreading

In real life, some people infect many others and others don't spread the disease at all (Kupferschmidt Science 2020: https://www.sciencemag.org/news/2020/05/why-do-some-covid-19-patients-infect-many-others-whereas-most-don-t-spread-virus-all). In fact, the latter is the norm, most people do not transmit. Frieden (Em Inf Dis 2020, see ***below***) noted that there have been multiple reports of superspreading events, which are associated with both explosive growth early in an outbreak and sustained transmission in later stages. For instance, Walker (Euro Surv 2020, see ***below***) whole-genome sequenced 55 SARS-CoV-2 isolates from Germany and found that the genetic structure of the outbreak in Heinsberg indicates a clonal origin, reflecting superspreading dynamics from mid-February during the carnival season.

These observations reflect a major limitation of the concept of R_0, the basic reproductive number, which is presented as a mean or median value and does not capture the heterogeneity of transmission among infected persons. For this

reason, in addition to R, the dispersion factor (k) describes how much a disease clusters. The lower k is, the more transmission comes from a small number of people. It has been estimated that SARS, in which superspreading played a major role, had a k of 0.16. The estimated k for MERS is about 0.25. In the flu pandemic of 1918, in contrast, the value was about one, indicating that clusters played less of a role.

Estimates of k for SARS-CoV-2 vary. In January, Julien Riou and Christian Althaus at the University of Bern simulated the epidemic in China for different combinations of R and k and compared the outcomes with what had actually taken place. They concluded that k for COVID-19 is somewhat higher than for SARS and MERS. However, in a recent preprint, Kucharski estimated that k for COVID-19 is as low as 0.1. Debora MacKenzie (New Scientist 2020, see ***below***) also referred to modelling data suggesting that only 10 per cent of cases are responsible for 80 per cent of transmission. Based on 135 cases in Tianjin, China, and utilizing a heterogeneous transmission model with branching process along with a negative binomial offspring distribution, Zhang (Int J Environ Res Public Health 2020, see ***below***) estimated k to 0.25 (95% CI: 0.13-0.88).

Lemieux (manuscript on medRxiv, see ***below***) studied two superspreading events that occurred in the USA. The first large cluster was recognized in the context of an international business conference held from February 26-27: more than 90 cases were associated with the conference and all 28, which were genotyped, formed a "monophyletic cluster", containing a C2416T signature polymorphism, which apparently originated from Europe and subsequently spread in Boston, making up 35 % of all 744 genomes outside the conference. This 2416T/G26233T variant was subsequently exported from Boston to several US states, including Virginia, North Carolina, and Texas, and to other countries, including Australia, Sweden, and Slovakia. A second more limited superspreading event at a skilled nursing facility in the Boston area involved 82/97 (85%) of the residents and 36/97 (37%) of the staff as detected by RT-qPCR. Of these SARS-CoV-2 cases, 75 comprised a single cluster of closely related genomes (59 identical), all containing a G3892T mutation.

Most recently, a very large study by Laxminarayan (Science 2020, see ***below***) that analysed data from the Indian states of Tamil Nadu and Andhra Pradesh, which have developed rigorous contact tracing and testing systems, concluded in 5% of infected individuals accounting for 80% of cases .

Transmission by asymptomatic or pre-symptomatic subjects

Numerous reports provide data indicating that asymptomatic (or pre-symptomatic) subjects can transmit COVID-19 with high efficiency (Chang Lancet Resp Med 2020, see ***below***). The possibility of transmission by asymptomatic individuals is a critical question, as it directly impacts public health responses to the epidemic.

The following evidence was obtained both from epidemiological observations and laboratory testing of asymptomatic subjects during the first weeks of the epidemic:

- A boy aged 10 years who was infected with COVID-19 had no symptoms but had visible changes in lung imaging and blood markers of disease.
- Another patient undergoing surgery in a hospital in Wuhan infected 14 health-care workers (HCWs) even before fever onset.
- A patient who travelled from Shanghai to attend a meeting in Germany was subclinical until on the flight back to China. However, two of this patient's close contacts and another two patients attending the meeting without close contact were found to be infected with COVID-19.
- Yu (J Inf Dis 2020, see ***below***) reported on a familial cluster of four patients in Shanghai, of which one was an 88 year-old man with moving difficulties who was only exposed to his asymptomatic family members who developed symptoms later

- Hoehl (NEJM 2020, see ***below***) reported that in the effort to evacuate 126 people from Wuhan to Frankfurt, a symptom-based screening process was ineffective in detecting SARS-CoV-2 infection in 2 persons who later were found to have evidence of SARS-CoV-2 in a throat swab.
- Zhou (NEJM 2020, see ***below***) analysed the viral load in one asymptomatic patient and found it similar to that in symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients.
- Bai (JAMA 2020, see ***below***) described a case of transmission from a presumed asymptomatic carrier with one positive PCR, but normal chest CT findings.
- Luo (Chin Med J 2020, see ***below***) identified a confirmed case of asymptomatic SARS-CoV-2 infection in a 50-year old woman. Despite largely normal laboratory and chest CT findings, her persistent positivity of the virus nucleic acid in her throat swabs and anal swabs for at least 17 days suggested that she was very likely a healthy carrier.
- Tang (Emerg Infect Dis 2020, see ***below***) reported on an asymptomatic child who was positive for SARS-CoV-2 by RT PCR in a stool specimen 17 days after the last virus exposure. The child was virus positive in stool specimens for at least an additional 9 days.
- Kam (Clin Inf Dis 2020, see ***below***) described a 6-month-old infant with COVID-19, who had persistently positive nasopharyngeal swabs to day 16 of admission, but no clinical signs or symptoms apart from a single transient temperature of 38.5°C.
- Pan (Lancet Inf Dis, see ***below***) described two individuals who were under active surveillance because of a history of exposure to infected patients and showed positive results on RT-PCR a day before disease onset.
- Tong (Emerg Infect Dis. 2020, see ***below***) described 2 infections resulting from contact with a potentially pre-symptomatic traveller from the city of Wuhan.
- Huang (J Inf 2020, see ***below***) monitored a cluster of close-contacts of a 22-year-old male with laboratory-confirmed COVID-19 in Anhui Province.
- Day (BMJ 2020, see ***below***) also reported the story of an Italian village, where identifying and isolating asymptomatic people helped eliminate the virus.

A more recent review by Han (Int J Inf Dis 2020, see ***below***) provided the evidence that asymptomatic infections can result in person-to-person transmission, and suggested that the virus can be transmitted by asymptomatic patients for at least two consecutive generations, indicating its strong infectivity. A set of studies aimed at quantifying the role of transmission by asymptomatic vs. symptomatic subjects. Du (Em Inf Dis 2020, see ***below***) analyzed 468 infector-infectee pairs with confirmed COVID-19 cases reported in China between January 21, 2020, and February 8, 2020. Interestingly, 12.1% of reports indicated pre-symptomatic transmission.

He (Nat Med 2020, see ***below***) reported temporal patterns of viral shedding in 94 patients with laboratory-confirmed COVID-19 and modelled COVID-19 infectiousness profiles from a separate sample of 77 infector-infectee transmission pairs. The highest viral load was observed in throat swabs at the time of symptom onset, and the authors inferred that infectiousness peaked on or before symptom onset. The authors estimated that 44% (95% confidence interval, 25-69%) of secondary cases were infected during the index cases' presymptomatic stage.

Buitrago-Garcia (manuscript on medRxiv, see https://www.medrxiv.org/content/10.1101/2020.04.25.20079103v3) addressed the topic with a living systematic review and meta-analysis focused on three questions: 1. amongst people who become infected with SARS-CoV-2, what proportion does not experience symptoms at all during their infection? 2. Amongst people with SARS-CoV-2 infection who are asymptomatic when diagnosed, what proportion will develop symptoms later? 3. What proportion of SARS-CoV-2 transmission is accounted for by people who are either asymptomatic throughout infection, or pre-symptomatic? A total of 94 studies was included. The overall estimate of the proportion of people who become infected with SARS-CoV-2 and remain asymptomatic throughout infection was

20% (95% CI 17-25) with a prediction interval of 3-67% in 79 studies that addressed this question. There was some evidence that biases in the selection of participants influence the estimate. In seven studies of defined populations screened for SARS-CoV-2 and then followed, 31% (95% CI 26-37%, prediction interval 24-38%) remained asymptomatic. The proportion of people that is pre-symptomatic could not be summarised, owing to heterogeneity. The secondary attack rate was slightly lower in contacts of people with asymptomatic infection than those with symptomatic infection (relative risk 0.35, 95% CI 0.10-1.27). Modelling studies fit to data found a higher proportion of all SARS-CoV-2 infections resulting from transmission from pre-symptomatic individuals than from asymptomatic individuals.

Transmission by recovered patients

Lan (JAMA 2020, see ***below***) reported data suggesting that at least a proportion of recovered patients still may be virus carriers. In this study four patients with COVID-19 who met criteria for hospital discharge or discontinuation of quarantine in China (absence of clinical symptoms and radiological abnormalities and 2 negative RT-PCR test results) had positive RT-PCR test results 5 to 13 days later, while they were continuing the quarantine protocol at home for 5 days. All patients had 3 repeat RT-PCR tests performed over the next 4 to 5 days and all were positive. An additional RT-PCR test was performed using a kit from a different manufacturer and the results were also positive for all patients. The patients continued to be asymptomatic by clinician examination and chest CT findings showed no change from previous images. They did not report contact with any person with respiratory symptoms. No family member was infected.

Ling (Chin Med J 2020, see ***below***) analysed, in 66 convalescent patients, the clearance time and factors influencing viral RNA detection in different samples from patients with COVID-19. A majority of patients had a longer duration until stool specimens were negative for viral RNA than for throat swabs, with a median delay of 2.0 (1.0-4.0) days. Only 6.9% urine samples were positive for viral nucleic acid; viral RNA was still present in three patients' urine specimens after throat swabs were negative. Using a multiple linear regression model ($F = 2.669$, $P = 0.044$, and adjusted $R2 = 0.122$), the analysis showed that the CD4+ T lymphocyte count may help predict the duration of viral RNA detection in patients' stools ($t = -2.699$, $P = 0.010$). The duration of viral RNA detection from oropharyngeal swabs and faecal samples in the glucocorticoid treatment group was longer than that in the non-glucocorticoid treatment group (15 days vs. 8.0 days, respectively; $t = 2.550$, $P = 0.013$) and the duration of viral RNA detection in faecal samples in the glucocorticoid treatment group was longer than that in the non-glucocorticoid treatment group (20 days vs. 11 days, respectively; $t = 4.631$, $P < 0.001$).

Chen (Int J Inf Dis 2020, see ***below***) reported a confirmed case of COVID-19 whose oropharyngeal swab test of SARS-CoV-2 RNA turned positive during convalescence.

Xing (Eurosurv 2020, see ***below***) also reported detection of RNA in two asymptomatic cases out of 62 recovered patients (3.23%). Mao (Int J Inf Dis 2020, see ***below***) similarly reported two cases of positive RT-PCR in asymptomatic (recovered) patients. Among the recurrence cases described by Jiang (J Inf 2020, see ***below***), one case had significant post-discharge clinical symptoms and discomfort for nine days, one case had a mild cough, and 4 cases were asymptomatic with positive RT-PCR nucleic acid test.

Yuan (Clin Inf Dis 2020, see ***below***) provided additional evidence of virus shedding from recovered patients. The study population included 172 discharged COVID-19 patients from Jan 23th 2020 to Feb 21th 2020, of which 25 patients (total 14.5%) subsequently developed a positive RT-PCR result. These 25 patients (median age of 28 years) had an average of 7.32±3.86 days from their last negative RT-PCR result to turning positive again.

A study by Tang (Infect Control Hosp Epidemiol. 2020, see ***below***) showed that among all 209 discharged COVID-19 patients in Shenzhen between January 23 and February 21, 2020, 9 (4.3%) patients showed RT-PCR positive in throat

swabs, 13 (6.2%) patients showed RT-PCR positive in anal swabs, and 22 (10.5%) positive in either type. The time between discharge and positive RT-PCR tests was 4.7 days on average.

Of note, A case report by Qu (Trav Med Inf Dis 2020, see ***below***) pointed to the importance of the specimen choice. Both a throat swab and sputum were collected before the patient was discharged. SARS-COV-2 nucleic acid was still detectable in sputum while the throat swab was negative.

Human to animal transmission and risk of reverse spillover

As SARS-CoV-2 infections are now widely distributed in the human population, there is a possibility for some animals to become infected through close contact with infected humans. Evidence of "reverse zoonotic" transmission, sometime referred to as "spillback," from people to wildlife and domestic animals is widespread (Messenger PLoS ONE 2014, see ***below***); however, systematic surveys to determine the proportion of emerging infectious diseases that spill back into novel wildlife hosts are lacking (Olival 2020 PLoS Pathogen 2020, see ***below***). Infection of animals with SARS-CoV-2 may have implications for animal health and welfare, and for wildlife conservation. Conservationists and health officials are, therefore, confronted with the challenge of informing the public about the potential health risks associated with bats and other potential animal hosts of SARS-CoV-2 without eroding already limited support for their conservation. This complex problem requires an integrated, transdisciplinary research agenda to support the design of evidence-based guidance and action plans on how to minimize zoonotic health risks while supporting bats and their associated ecosystem services (Rocha Anim Conserv 2020, see ***below***). Wildlife health capacity is as much about protecting wild animal populations and biodiversity as it is about protecting people and as such there is a need for a global wildlife health authority (https://www.iucn.org/crossroads-blog/202009/it-time-a-global-wildlife-health-authority).

Understanding the risk of exposure of humans or animals to SARS-CoV-2 from animals and their products is essential for containing virus spread, prioritizing research, design informed conservation policies, protecting food systems, and informing national One Health investigations and mitigation measures. The FAO has issued a "Qualitative Exposure Assessment" tool which provides a comprehensive review of available scientific evidence and assessment of exposure risk from different wild or domestic animal species. Results can inform country-level risk assessment and provide the evidence base for targeted SARS-CoV-2 investigations in animals and mitigation options (El Masry 2020, see ***below***). Moreover, the impact of the reduced human mobility on wildlife during the lockdown enforced in many countries in response to the pandemic may enable a detailed, mechanistic understanding of human–wildlife interactions that could inspire realistic, evidence-based proposals for improving human–wildlife coexistence (Rutz 2020, see ***below***). An internationally recognized standard for managing wildlife trade on the basis of known disease risks should be established. A decentralized network could improve feedback between those who screen samples and those who curate data to bolster the safety of wildlife and humans, a fundamentally "One Health" approach. This would increase localized knowledge of emerging infectious diseases risks, provide earlier warnings and faster global responses to spillovers, and inform wildlife trade policy. This model is more robust to shifting political landscapes and funding and does not ignore the role of advanced regional research laboratories, which also provide vital targeted pathogen screening (Watsa Science 2020, see ***below***). Their analysis and Dobson's (Science 2020, see ***below***) suggest that the associated costs of preventive efforts (preventing deforestation, regulating wildlife trade and zoonotic disease surveillance) would be substantially less than the economic and mortality costs of responding to these pathogens once they have emerged. The gross estimated costs of the actions total $22 to $31 billion per year. Reduced deforestation has the ancillary benefit of around $4 billion per year in social benefits from reduced greenhouse gas emissions, so net prevention costs range from $18 to $27 billion per year. In comparison, COVID-19 has shown us the immense potential cost of a pandemic. The world may lose at least $5 trillion in GDP in 2020, and the willingness to pay for the lives lost constitutes many additional trillions (Dobson Science 2020 ; supplementary material, see ***below***). These costs exclude

the rising tally of morbidity, deaths from other causes due to disrupted medical systems, and the loss to society of foregone activities due to social distancing.

On 2nd June 2020, the International Union for Conservation of Nature (IUCN) issued a comprehensive "Questions and answers on COVID-19 and nature conservation" addressing the impact of the pandemic on the conservation of threatened species (e.g. non-human primates, bats), and indigenous communities and recommending conservation measures to minimise the risk of zoonotic diseases being transmitted to humans (https://www.iucn.org/covid-19-resources/questions-and-answers-covid-19-and-nature-conservation). The Office for Epizootics (OIE) has produced a complete special edition bulletin on COVID-19 which is regularly updated (https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/A_Q%26A_COVID-19.pdf). OIE also published a document to guide testing of human diagnostic specimens in veterinary laboratories (https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/A_Guidance_for_animal_health_laboratories_1April2020.pdf) to support the evaluation of human-animal contacts. The European Commission issued a comprehensive Q&A document tackling COVID-19 in farmed and domestic animals including policies related to the responsibilities of the veterinary authorities in this public health crisis (https://ec.europa.eu/food/sites/food/files/animals/docs/ah_covid-19_qandas_en.pdf?wtclear=laco).

Surrogate virus neutralization test (sVNT), which is species and isotype independent, has an advantage over VNT in that it does not use live virus and can therefore be conducted in a biosafety level 2 (BSL2) laboratory. It has been presented as an option to test for the presence of antibodies to SARS-CoV-2 in all animal species. The OIE's organisation response to the pandemic has also been communicated in a special bulletin (https://oiebulletin.com/wp-content/uploads/2020/05/OIE-News-May2020-Special-Edition-COVID-19-main-news-article_withoutstatement.pdf), which outlines the development of special ad-hoc advisory groups for animal health laboratories and animal health surveillance. According to OIE's Terrestrial Animal Health Code, the infection of animals with SARS-CoV-2 meets the criteria of an emerging disease ("animal" is defined as "a mammal, reptile, bird, or bee"). Therefore, any case of infection of animals with SARS-CoV-2 should be reported to the OIE in accordance with the OIE Terrestrial Animal Health Code and include information about the species, diagnostic tests, and relevant epidemiological information.

On April 1st, the US Fish and Wildlife Service sent out a directive advising scientists to suspend all bat studies and take appropriate sanitary precautions and safety measures (PPEs, disinfection of equipment) when working with wildlife in general, concerned that researchers could spread the disease to bats and other wild animals (https://www.usgs.gov/media/files/nwhc-operations-during-covid-19-pandemic-and-info-about-coronaviruses). This is supported by the global distribution and host range of β-CoV evolutionary lineages which suggests that over 40 species of temperate-zone North American bats could be immunologically naïve and susceptible to infection by SARS-CoV-2 (Olival PLoS Pathogen 2020, see ***below***). On 21st August 2020, Guidelines for Working with Free-Ranging Wild Mammals in the Era of the COVID-19 Pandemic were released by OIE and the IUCN Wildlife health Specialist Group (http://www.iucn-whsg.org/COVID-19GuidelinesForWildlifeResearchers). These recommendations are based on first principles of biosecurity and hygiene, current knowledge of human-to-animal SARS-CoV-2 transmission and the precautionary principle (minimize contact with animals, assess your own health condition, and protect yourself). It also provides useful references to taxa specific guidelines (felid and small carnivores, apes, bats). A real time on-line resource for people working at the human - NHP interface has also been launched in the view to create a community of practice, connecting relevant facts, experts and resources from several professional communities (human health, captive, sanctuary, and in situ conservation 'facilities' and sites) to assist with response and management of the SARS-CoV-2 epidemic (https://umnadvet.instructure.com/courses/324). A comprehensive paper (Zhang Transbound Emerg Dis 2020, see ***below***) reviewed the current understanding about animal coronaviruses and SARS-CoV-2 for their emergence, transmission, zoonotic potential, alteration of tissue/host tropism, evolution, status of vaccines, and surveillance. The paper also provides guidance for control of COVID-19 and preventative strategies for possible future

outbreaks of zoonotic coronavirus via cross-species transmission. The risk of introduction of SARS-CoV-2 in Antarctica wildlife is discussed in a preprint (Barbosa, manuscript on Preprints: https://www.preprints.org/manuscript/202008.0478/v1) and list a series of guidelines for visitors. This follows the story of a SARS-CoV-2 positive tourist who visited several sites along the Antarctic Peninsula, which raised concerns regarding the potential human introduction of the virus on this continent through research activities or tourism. Cold conditions can potentially facilitate fomite transmission, especially via scientific equipment used by several people or in contact with both humans and other animals. Based on score for the binding affinity of their ACE2 receptor (Damas, Proc Natl Acad Sci USA 2020, see ***below***), transmission of SARS-CoV-2 to Antarctic birds seems unlikely while cetaceans appear to have the highest risk of SARS-CoV-2 infection amongst Antarctic wildlife. The potential role of bats as hosts of SARS-CoV and SARS-CoV-2 has been challenged by Yan (manuscript on Biorxiv : https://doi.org/10.1101/2020.09.08.284737). The authors analysed genetic and functional ACE2 orthologs from 46 bat and argued that many bat species are not potential hosts of SARS-CoV and SARS-CoV2. Their results are partly consistent with Damas (Proc Natl Acad Sci USA 2020, see ***below***) who confirmed the role of critical residues of bat ACE2 in supporting SARS-CoV-2 entry in 19 bats species. However, disparities between *in silico* analyses and functional experiments confirm the complexity of ACE2 functionality and the importance of complementary methodologies as our understanding of ACE2 sequences and structures is yet incomplete.

Fenton (Facets 2020, see ***below***) summarized the essential ecosystem services provided by bats, and how people's perceptions may be an additional threat to bats worldwide following the emergence of SARS-CoV-2. As such, reverse spillover events - the risk of SARS-COV-2 being introduced into endemic wildlife from humans - raises an additional concern and another serious public health threat. Preventing human-to-wildlife SARS-CoV-2 transmission is important for protecting these (sometimes endangered) animals from disease, but also to avoid establishment of novel SARS-CoV-2 reservoirs in wild animals. The risk of repeated re-infection of humans from such a wildlife reservoir could severely hamper SARS-CoV-2 control efforts (Gryseels, manuscript on Preprints: https://www.preprints.org/manuscript/202005.0141/v1). While containing the human outbreak is a priority, estimating the transmission potential and introduction of SARS-COV-2 in domestic and wild animals similarly requires immediate action, especially when considering viral discharge in the environment and survival times.

The use of network- and trait-based statistical models to predict suitable wildlife hosts for SARS-CoV-2 (e.g. pangolins, civets, bats) is presented as a cost-efficient strategy to optimize reservoir research and prioritize taxa sampling (Becker, manuscript on bioRxiv: https://doi.org/10.1101/2020.05.22.111344). Several reviews on the risk of the potential modes and risk of human-to-domestic animals and wildlife transmission of SARS-CoV-2 have been published recently (Mahdy, manuscript on Preprints: https://www.preprints.org/manuscript/202004.0192/v1; McNamara Vector Borne Zoonotic Dis 2020, see ***below***; Gryseels, manuscript on Preprints: https://www.preprints.org/manuscript/202005.0141/v1).

As of 3rd July 2020, the animal species for which information on natural or experimental infection with SARS-CoV-2, and for which infection can lead to transmission between animals, included cats (domestic), tigers and lions, ferrets, minks, Egyptian fruit bats (*Rousettus aegyptiacus*), Golden Syrian hamsters, Macaques (*Macaca fascicularis* and *Macaca mulatta*) (https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/A_Factsheet_SARS-CoV-2.pdf). Two preprints addressing the risk of reverse zoonosis in North America (Griffin, manuscript on bioRxiv, see: https://doi.org/10.1101/2020.07.25.221291 and Fagre, manuscript on bioRxiv, see: https://doi.org/10.1101/2020.08.07.241810) subsequently added relevant information to the topic. The former demonstrated that adult deer mice (*Peromyscus maniculatus*) are susceptible to SARS-CoV-2 infection following intranasal exposure to a human isolate, resulting in viral replication in the upper and lower respiratory tract with little or no signs of disease. The later infected experimentally deer mice with SARS-CoV-2 and found detectable viral RNA for up to 21 days in oral swabs and 14 days in lungs while no conspicuous signs of disease were observed and no deer

mice succumbed to infection. Contact transmission occurred from infected to naive deer mice showing for the first time sustained natural transmission in an endemic rodent outside Asia, and determining the potential role as secondary reservoir host in a North American rodent, which could lead to periodic outbreaks of COVID-19. Schlottau (The Lancet Microbe 2020, see https://europepmc.org/article/pmc/pmc7340389) experimentally investigated the susceptibility of potential animal hosts and the risk of anthropozoonotic spill-over infections by intranasally inoculating fruit bats (*Rousettus aegyptiacus*), ferrets (*Mustela putorius*), pigs (*Sus scrofa domesticus*), and chickens (*Gallus gallus domesticus*) with SARS-CoV-2. Pigs and chickens were not found susceptible to SARS-CoV-2. All swabs, organ samples, and contact animals were negative for viral RNA, and none of the pigs or chickens seroconverted. Fruit bats had a transient infection, with virus detectable by RT-qPCR, immunohistochemistry, and in situ hybridisation in the nasal cavity, associated with rhinitis. Viral RNA was also identified in the trachea, lung, and lung-associated lymphatic tissue. One of three contact bats became infected. More efficient virus replication but no clinical signs were observed in ferrets, with transmission to all three direct contact animals. Mild rhinitis was associated with viral antigen detection in the respiratory and olfactory epithelium. Both species developed SARS-CoV-2-reactive antibodies reaching neutralising titres of up to 1/1024 after 21 days.

A subsequent experimental study somewhat contradicted these previous reports which suggested that pigs are not susceptible to SARS-CoV-2 infection. Using a ten-fold higher viral dose for inoculation, Pickering (manuscript on bioRxiv : https://doi.org/10.1101/2020.09.10.288548) found that following oronasal inoculation, SARS-CoV-2 persisted in swine for at least 13 days. Viral RNA was detected in group oral fluids and nasal wash from at least two animals while live virus was isolated from a pig. Further, antibodies could be detected in two animals at 11 and 13 days post-infection. The authors therefore defined domestic swine as a species susceptible to SARS-CoV-2 infection, albeit at low level.

Naturally acquired infections in animals

Current evidence indicates that some animal species can become infected with SARS-CoV-2 under natural conditions. These events appear to be rare and sporadic and are predominantly epidemiologically linked to confirmed human cases of COVID-19. However, there is limited testing and surveillance data available at this time. With over 150 reports of animal infection by SARS-CoV-2 with economical, conservation, veterinary and public health impact, Mobasheri is calling for One Health and comparative medicine (Front Vet Sci 2020, see ***below***).

The US CDC has now issued clear criteria to guide evaluation and laboratory testing for SARS-CoV-2 in animals (https://www.cdc.gov/coronavirus/2019-ncov/animals/animal-testing.html).

Table 8 Criteria to Guide Evaluation and Laboratory Testing for SARS-CoV-2 in Animals (from https://www.cdc.gov/coronavirus/2019-ncov/animals/animal-testing.html)

Criteria	Epidemiological Risk		Clinical Features
A	Animal with history of exposure to a person or animal suspected or confirmed to be infected with SARS-CoV-2.	AND	Animal has clinical signs suspicious of SARS-CoV-2 infection.
B	Animal with exposure to a known high-risk environment (i.e., where human cases or animal cases have occurred), such as a residence, facility, or vessel (e.g. nursing home, prison, cruise ship).		
C	Threatened, endangered or otherwise imperiled/rare animal in a rehabilitation or zoological facility with possible exposure to SARS-CoV-2 through an infected person or animal.	AND	Animal is asymptomatic; OR Animal has clinical signs suspicious of SARS-CoV-2 infection.

D	Animals in a mass care or group setting (e.g., farm, animal feeding operation, animal shelter, boarding facility, zoo, or other animal holding) including companion animals, livestock, and other species, where their exposure history to people with COVID-19 is unknown.	AND	A cluster of animals show clinical signs suspicious of SARS-CoV-2 infection.

Although the clinical spectrum of illness for this virus remains largely undefined in animals, clinical signs more likely to be compatible with SARS-CoV-2 infection in mammalian animals may include a combination of the following: fever, coughing, difficulty breathing or shortness of breath, lethargy, sneezing, nasal discharge, ocular discharge, vomiting and diarrhoea. The exposure is defined as i) being within approximately 2 meters of a person with suspected or confirmed COVID-19 starting from 2 days before the person's illness onset (or, for asymptomatic human patients, 2 days before positive specimen collection) until the time the person is isolated, and ii) having direct contact with infectious secretions from a person with suspected or confirmed COVID-19 starting from 2 days before the person's illness onset (or, for asymptomatic human patients, 2 days before positive specimen collection) until the time the person is isolated. Direct contact could include an animal being coughed, sneezed, or spit on by an infected person or sharing food or consuming something that was recently contaminated with an infected person's mucous or saliva.

There have been multiple notifications to OIE of non-human animals testing positive to SARS-CoV-2 by PCR, and both individual animal cases and farm outbreaks have been reported in the scientific media. The species and location of reported cases are shown in ***Table 9*** below.

Table 9 Numbers of animals, by species and country, that have tested positive for SARS-CoV-2

Animal species affected	ASIA		AMERICAS	AFRICA	EUROPE								TOTALS
	HK	JA	USA**	SA	BE	NL	DK	FR	ES	DE	UK	RU	
DOMESTIC													**37**
Dogs	3	12	4+1^			1^†	1†						20 (+2^)
Cats	4		6		1*			2*	1*	1*	1	1	17
ZOO													**9**
Tigers			5										5
Lions			3										3
Puma				1									1
FARMED													**163**
Mink			9			64#	89#		1				163#

Legend : HK, Hong Kong; JA, Japan ; USA, United states of America; SA, South Africa; BE, Belgium ; NL, the Netherlands; DK, Denmark; FR, France; ES, Spain ; DE, Germany ; UK, United Kingdom and RU, Russia
† Not reported to the OIE
** Unofficially reported to the OIE*
*** The U.S. Department of Agriculture (USDA) maintains a list of all animals with confirmed infections with SARS-CoV-2 in the United States (https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/sa_one_health/sars-cov-2-animals-us)*
^ Antibody positive only
 # Number of affected farms. Number of animals not reported.

Infection of any animal with SARS-CoV-2 should be notified to the OIE as an emerging disease in accordance with Chapter 1.1 of the OIE Terrestrial Animal Health Code.

The OIE have released the following suggested case definitions for SARS-CoV-2 infections in animals (OIE Report, https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/Sampling_Testing_and_Reporting_of_SARS-CoV-2_in_animals_final_7May_2020.pdf):

An animal should be classified as a suspected case of SARS-CoV-2 infection if:

- *The animal has clinical signs suggestive of SARS-CoV-2 infection, including but not limited to; nasal discharge, respiratory distress, coughing, vomiting or gastrointestinal disease. As in humans, mild or asymptomatic infections are likely to occur and should be considered in epidemiological investigations; and*
- *All other likely differential diagnostic aetiologies have been effectively ruled out by a veterinarian; and*
- *The animal has an epidemiological link with a confirmed human COVID-19 patient, SARS-CoV-2 infected animal or suggestive case history indicating potential exposure.*

An animal should be classified as a confirmed case of SARS-CoV-2 infection if:

- *SARS-CoV-2 has been isolated from a sample[15] taken directly from an animal; or*
- *Viral nucleic acid has been identified in a sample taken directly from an animal, giving cause for suspicion of previous association or contact with SARS-CoV-2, by:*
    a) *Targeting at least two specific genomic regions at a level indicating presence of infectious virus; or*
    b) *Targeting a single genomic region followed by sequencing of a secondary target.*

At least 20 domestic dogs and 17 domestic cats have tested positive to SARS-CoV-2 by RT-PCR and/or antibody-capture ELISA, following close contact with confirmed (or suspected) COVID-19 human patients (OIE WAHID, https://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/WI; Zhang manuscript on bioRxiv: https://doi.org/10.1101/2020.04.01.021196). Seroconversion has been detected in some cases. So far, no cases of cat- or dog-to-human transmission have been reported.

In a recent study on the potential epidemiological role of domestic cats and dogs, a higher seroprevalence of SARS-CoV-2 antibodies (microsphere immunoassays (MIA) targeting anti-SARS-CoV-2 IgGs and a retrovirus-based pseudoparticle assay targeting SARS-CoV-2 neutralizing antibodies), ranging from 21% to 53% was detected (Fritz, manuscript on bioRxiv : https://www.biorxiv.org/content/10.1101/2020.09.22.307751v1). The seropositivity among pets from COVID-19 positive households (10/47) was significantly greater compared to households with unknown status (1/38). Though these results do not prove that all positive animals were infected with SARS-CoV-2, the much greater seroprevalence in animals from COVID-19 positive households provide strong evidence that pets have been infected with SARS-CoV-2.

This study along with multiple punctual reports issued between January and October 2020 strongly suggest that globally – due to the unsystematic testing of domestic and wild animals – there is a dramatic underestimation of the prevalence and incidence of SARS-CoV-2 in animals, and that the epidemiological role of animal in SARS-CoV-2 transmission is far from being understood. The amount of effort dedicated to control and test human in priority – while obviously justified – have however overlooked the broader epidemiological complexity of SARS-CoV-2 transmission which should be tackled using a One Health approach. These crucial gaps - 8 months after the official recognition of the COVID-19 pandemic by WHO - therefore limit our abilities to control the emergence and re-emergence of SARS-CoV-2 in both human and animal populations worldwide. There is an urgent need to re-assess the panzootic status of SARS-CoV-2.

Details of the detected cases in dogs and cats include:

- **Dog (Pomeranian, Hong Kong)**
  (ProMED-mail, Archive Number: 20200326.7146438, https://promedmail.org/promed-post/?id=20200326.7146438; OIE WAHID, https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?reportid=33762). A 17-year-old Pomeranian was placed in quarantine in Hong Kong on the 26th February 2020, after its 60-year-old owner was

[15] Samples for virus isolation and viral nucleic acid are preferably nasal swab, oropharyngeal swab, nasal washing, tracheal swab and/or a rectal sample may be taken, or a faecal sample may be used in situations where direct sampling is not possible due to risks to the animal or testing staff; or from internal organs collected post-mortem.

diagnosed with COVID-19 the previous day. Prior to entry to the quarantine facility, the animal was examined by a veterinarian and found to be clinically well. Nasal, oral, rectal swabs and a fresh faecal sample were collected and tested for SARS-CoV-2. The nasal and oral swab samples collected at this initial examination tested positive to SARS-CoV-2 by real time RT-PCR, and viral gene sequencing was performed. The viral sequence was highly similar to SARS-CoV-2 sequences detected in humans in close contact with the dog, indicating that human-to-animal transmission was the most likely cause of infection.

The animal tested positive to SARS-CoV-2 by PCR over a period of 12 days, and was subsequently shown to have developed a neutralising antibody response by PRNT. No clinical signs of coronavirus had been detected throughout the period of testing. The dog is assumed to have been infected through close contact with its infected owner. The animal was released from quarantine following successive negative PCR tests, however it died 2 days later. It has been widely reported that the death was suspected to be due to an unrelated geriatric disease, however the definitive cause of death was unable to be determined as the owner declined an autopsy on the dog.

- **Dog (German Shepherd, Hong Kong)**

  (OIE WAHID, https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=33892).

  On the 19th March, a second dog belonging to a COVID-19 patient tested positive in Hong Kong. A 2-year-old German Shepherd and a 4-year-old mixed breed dog from the same household had been placed under quarantine on 18 March 2020 after their owner was hospitalized due to COVID-19 infection. Neither dog showed any clinical signs of infection (Almendros Vet Rec 2020, see ***below***).

  Nasal, oral and rectal swab samples were collected from both animals on admission to the facility (18th March), and again on 19th and 20th March. Samples from the German Shepherd tested positive by real time RT-PCR at all 3 timepoints, and seroconversion was confirmed by PRNT. Virus isolation was also successful. The mixed breed dog was negative on all testing. Subsequent swab samples collected over the following 10 days were negative. Based on the epidemiological history it is suspected that this is a case of human-to-animal transmission, however there is no publicly available sequencing results to support this.

- **Cat (Belgium)**

  (ProMed Archive number: 20200327.7151215, https://promedmail.org/promed-post/?id=20200327.7151215; OIE statement,https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/Belgium_28.03.20.pdf).

  The Belgian Chief Veterinary Officer reported on 18th March that a cat had tested positive to SARS-CoV-2. The cat's owner was confirmed to have COVID-19 and started home confinement immediately upon their return from Italy. One week after the owner's return, the cat started showing clinical signs of respiratory and digestive disease, including anorexia, diarrhoea, vomiting, coughing and superficial breathing.

  Samples of the cat's faeces and vomit were confirmed positive for SARS-CoV-2 viral RNA by PCR and sequencing. High viral loads have been reported and are suggestive of a productive infection occurring in the cat, but contamination of samples from the environment/owner cannot be ruled out because the samples were taken from the environment (and not directly from the animal) by the owner, who is not a technical expert. On 19th March, the FASFC requested an urgent opinion to the independent Scientific Committee established at the FASFC. According to this Committee, the elements reported do not allow confirmation of a productive viral infection in the cat, but it is suspected based on the PCR Ct values compatible with a high number of viral genome copies and clinical signs compatible with a coronavirus infection. The cat began to improve clinically nine days after the onset of clinical signs. No serological studies have been reported to date.

- **Cat (Domestic Short Hair, Hong Kong)**

(ProMED-mail Archive Number: 20200403.7179945, https://promedmail.org/promed-post/?id=20200403.7179945; OIE WAHID, https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=34221). On 31st March, The Hong Kong Government reported that a pet cat of a COVID-19 patient had tested positive for SARS-CoV-2. As was the case with previous detections in dogs in Hong Kong, the cat tested positive following veterinary examination and sampling on arrival at a quarantine facility. No clinical signs were observed. Nasal, oral and rectal swabs all tested positive for SARS-CoV-2 by real time RT-PCR. Repeat oral and nasal swab samples were also positive by PCR. Virus neutralising antibody was subsequently detected. Virus isolation attempts were unsuccessful. Successive negative swab samples were obtained during the quarantine period and the animal was eventually returned to its owner.

- **Cats (New York, USA)**
  (ProMED-mail, Archive Number 20200422.7256272 https://promedmail.org/promed-post/?id=7256272; CDC media release https://www.cdc.gov/media/releases/2020/s0422-covid-19-cats-NYC.html; OIE WAHID statement, https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?reportid=34086).
  On April 22, the CDC released a statement that two domestic cats in New York had tested positive to SARS-CoV-2. On April 23, the NVDL confirmed virus neutralising antibodies were detected in follow-up samples from both affected domestic cats. The two cats lived in separate parts of New York and the cases are not considered to be epidemiological linked. Both cats were displaying mild signs of respiratory disease, including sneezing and ocular discharge. Only one of the cats was owned by a confirmed COVID-19 patient, who tested positive prior to the cat developing disease. A second cat in this household has tested negative. It is unclear how the other animal became infected – the CDC press release states 'the virus may have been transmitted to this cat by mildly ill or asymptomatic household members or through contact with an infected person outside its home'. News reports suggest that a member of the household experienced a short respiratory illness approximately 1 week prior to the cat developing signs of disease, however it appears that the person was not tested for COVID-19. The cat is also reported to spend time outdoors and the possibility of exposure from the nearby area remains viable.
- **Cats (France)**
  (ProMED-mail Archive Number: 20200501.7289409, https://promedmail.org/promed-post/?id=7289409; https://www.vet-alfort.fr/images/Communication/CP/2020-05-01_-_CP_Chat_SRAS-cov2.pdf). On 30th April, the Deputy Head of the Animal Health Laboratory ANSES in France communicated to ProMED a preliminary report of a study investigating SARS-CoV-2 infections in cats owned by people suspected to have had COVID-19. Rectal and nasopharyngeal swabs were taken from each cat and tested by qRT-PCR, with any positives to be confirmed by the OIE Collaborating Centre at the Pasteur Institute in Paris. One cat, which had reportedly showed mild respiratory and digestive signs, tested positive for SARS-CoV-2 on its rectal swab, while its nasopharyngeal swab tested negative. A description of this case was provided by Sailleau (Transbound Em Dis 2020, see ***below***).
  A second French cat, from the city of Bordeaux, was reported by the National Veterinary School of Toulouse (France) to have positive for SARS-COV-2 on the 12th of May (ProMED-mail Archive Number: 20200513.7332909, https://promedmail.org/promed-post/?id=7332909). The cat lived in a household with people suspected of having contracted COVID-19 and developed a persistent cough that was non-responsive to antibiotic and anti-inflammatory treatment. A nasopharyngeal swab was positive on PCR, whilst rectal swabs were negative.
- **Cat (Germany)**
  SARS-CoV-2 infection has been reported in a cat in Germany following the death of its owner from COVID-19 (ProMED-mail Archive Number: 20200513.7332909, https://promedmail.org/promed-post/?id=7332909). The cat lived with its owner in a retirement home in which there is an ongoing COVID-19 outbreak. Two other cats living in the facility have tested negative. No clinical signs were observed in the infected cat. All 3 cats

have been transferred to a quarantine facility and despite being housed together, the non-infected cats have continued to return negative PCR results on follow-up sampling. The investigation is ongoing.

- **Cat (Spain)**
  On 11th May 2020, the Spanish Ministry of Agriculture, Fisheries and Food confirmed the first SARS-CoV-2 infection in a cat in the country but advised caution regarding the interpretation of the infection. The cat was taken to a veterinary facility on 22nd April 2020 as it was in respiratory distress (dyspnea and tachypnea), and upon examination was shown to have a mild anaemia and severe thrombocytopenia. At the radiographic level, a broncho-interstitial pattern with increased opacity of the lung was noted. The cat was euthanized due to its degrading condition and the body was sent for autopsy, which determined that the cat's death was caused by an underlying hypertrophic cardiomyopathy of probable genetic origin, not consistent with SARS-COV-2 viral infection. Nasal swabs, and one mesenteric lymph node were SARS-COV-2 positive by RTqPCR (3 markers tested). The cat belonged to a household with several family members previously diagnosed with COVID-19 in late April. However, the detection of SARS-CoV-2 RNA in several samples from the animal is suggested to be incidental, potentially associated with being in an environment contaminated by the virus, but in any case, not responsible for the clinical symptoms he was suffering from (https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/Nota_Gato%20SARS-CoC-2_spain.pdf).
- **Dog (Netherlands)**
  In her letter dated 15th May 2020, Dutch agriculture minister Carola Schouten reported that an eight-year-old American bulldog, owned by a COVID-19 patient, was euthanised on 30th April due to severe and deteriorating respiratory disease. Testing of samples did not detect SARS-CoV-2, but did identify antibodies to SARS-CoV-2 in the dog's blood. It was not reported whether the dog's death was attributed to SARS-CoV-2 or to another cause. The minister has since implemented requirements for veterinarians to report of suspected COVID-19 in animals, and laboratories to report positive test results, to the Netherlands Food and Consumer Product Safety Authority (NVWA). (https://www.rijksoverheid.nl/documenten/kamerstukken/2020/05/08/kamerbrief-stand-van-zaken-corona-en-dieren).
- **Cat (Russia)**
  On 26th May 2020, the OIE WAHID received a report of the first confirmed SARS-CoV-2 animal case in Russia, after throat and nasal swabs taken from a five-year-old cat tested positive by rRT-PCR on 22nd May (https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=34443). The PCR amplification products were detected by electrophoresis and subsequently underwent sequencing, which showed 100% correlation with the 232 bp N gene fragment OFR1ab of the SARS-CoV-2 virus. The cat is reportedly under quarantine, presumably at home in Moscow Oblast, but no details of the clinical condition of the cat or its owner have been provided.
- **Dog (New York, USA)**
  The USDA APHIS have confirmed that 2 dogs have tested positive to SARS-CoV-2 in Richmond County, New York State (https://www.aphis.usda.gov/aphis/newsroom/stakeholder-info/sa_by_date/sa-2020/sa-06/sars-cov-2-dog). One dog, a German Shepherd, initially tested positive by PCR at a private laboratory after presenting to a veterinarian with respiratory illness. This result was later confirmed by the National Veterinary Services Laboratories (NVSL). Serological testing by VNT confirmed the presence of antibodies. This is the first reported case of a dog with clinical disease consistent with COVID-19 testing positive to SARS-CoV-2 by PCR.
  A second dog in the household also tested serologically positive, indicating prior exposure, however no clinical signs were observed. One of the animals' owners was a confirmed COVID-19 patient.
- **Cat (Minnesota, USA)**

On 3rd June the OIE WAHIS reported a confirmed case of SARS-CoV-2 in a domestic pet in Minnesota, USA, from a household with known COVID-19 cases (https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=34548). The cat was showing clinical signs including depression, fever and harsh lung sounds, and tested positive for both SARS-CoV-2 and Mycoplasma felis – another potential respiratory pathogen – on initial testing. SARS-CoV-2 was confirmed by rRT-PCR and sequencing on 27th and 28th May 2020, respectively. A dog residing in the household appears to be healthy, but it was not reported whether the dog was also tested for SARS-CoV-2. The cat is reportedly being quarantined at home for 14 days, and both the cat and the owners are reported to be recovering well.

- **Cat (Illinois, USA)**
  A domestic cat from a known COVID-19 household in Illinois, USA, was reported to positive for SARS-CoV-2 on 10th June after developing respiratory illness. Clinical signs included fever, oral lesions and ulcerations on the tongue. Initial feline respiratory panel testing was negative to FIV and FeLV, and positive to feline coronavirus, which was later confirmed as SARS-CoV-2 by PCR and sequencing on 27th May. The cat is reported to be recovering (https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=34590).
- **Dog (Denmark)**
  On 20th June 2020, veterinary and Food Administration Minister in Denmark, COVID-19 infection was found in a family dog belonging to the 1st infected mink farm in Denmark. The nature of the testing is not known. The dog is being kept inside and avoid close contact with other animals and people outside the household by its owner as per recommendations of the authorities (https://mfvm.dk/nyheder/nyhed/nyhed/regeringen-igangsaetter-testprogram-efter-nyt-covid-19-fund-i-danske-mink/).
- **Dog (Texas, USA)**
  A Tarrant County dog was confirmed to be infected with SARS-CoV-2, the on 7 Jul 2020 by the U.S. Department of Agriculture (USDA) National Veterinary Services Laboratories (NVSL). The private veterinarian chose to test the dog for SARS-CoV-2 as a precautionary measure after its owners were confirmed to have COVID-19. The veterinarian reports the 2-year-old dog is healthy at this time (Promed Archive Number: 20200708.7554832).
- **Cat (Hong Kong)**
  On 24th July 2020, a cat which did not exhibit any relevant clinical signs and kept in the same household as a confirmed COVID-19 patient of Hong-Kong has been tested positive for SARS-CoV-2. The cat was placed under quarantine on 21 Jul 2020 after confirmation of a human case from the same household. Following veterinary examination, nasal, oral and rectal swab samples were taken; the oral sample was tested positive for SARS-CoV-2 by real time RT-PCR. As of 11th August, faecal sample was tested positive by real time RT-PCR. And the cat subsequently confirmed to be seropositive by a surrogate virus neutralisation test. A Siberian Husky dog kept in the same household of a close contact of a confirmed COVID-19 patient tested positive for SARS-CoV-2 by real time RT- PCR. None of the animals exhibited any specific clinical signs. Risk management measures are in place for all cases, including cleansing and disinfection of the premises, and proper personal hygiene and protection. (https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=35169).
- **Cat (United Kingdom)**
  On 27th July 2020, the Department for Environment, Food and Rural Affairs of the UK reported to OIE that a domestic cat from a COVID positive household in South England tested positive for SARS-CoV-2 by PCR. The cat was showing respiratory signs indicative of Feline Herpes Virus (FHV) and a swab was taken for confirmation in May and a SARS-CoV-2 test was undertaken as part of a surveillance project in a private

laboratory. The cat was co-infected with FHV and SARS-CoV-2. In July 2020, a new oral swab was negative, and the blood sample was positive to the virus neutralisation test. A second cat in the household was tested negative by PCR and virus neutralisation. The positive cat completely recovered (PCR negative and seropositive) (Promed Archive Number: 20200727.7617582 and reported to OIE: https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=35182.)

- **Cat (Louisiana, USA)**
  The Louisiana Department of Agriculture and Forestry (LDAF) received its 1st reported case of a SARS-CoV-2-positive dog in Louisiana. No details were given about clinical symptoms or household owner COVID status (Promed archive number : 20200805.7648734).
- **Dogs (Japan)**
  On 7th August, the Japan Ministry of Agriculture, Forestry and Fisheries (MAFF) reported SARS-CoV-2 infection in two dogs belonging to COVID-19 confirmed patients (https://www.oie.int/fileadmin/Home/MM/Japan_08.2020.pdf). The two dogs were brought to a private company in Japan that has been running a voluntary service to take care of companion animals owned by COVID-19 patients while the owners are in hospital or isolation. Newly arrived animals are kept in isolation until tested negative for SARS-CoV-2 by rRT-PCR. In late July, the throat swabs of 2 asymptomatic dogs were subjected to rRT-PCR which confirmed the dogs were positive for SARS-CoV-2. Positive samples were subsequently submitted to the National Institute for Infectious Diseases (NIID) and confirmed to be positive by rRT-PCR, RT-PCR and sequencing. Overall, since 26th July 2020, the Japan Ministry of Agriculture, Forestry and Fisheries (MAFF) reported SARS-CoV-2 infection in 12 dogs (1 in July, 9 in August, and 2 in September) to OIE
  (https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=35864).
- **Cat (Texas, USA)**
  On 8th August, 2020, Texas A&M researchers from the College of Veterinary Medicine & Biomedical Sciences (CVMBS) have identified 2 cats in Brazos County that tested positive for COVID-19. The team is working to understand how pets living in "high-risk" households may be impacted by COVID-19 by sampling pets, dogs and cats, whose owners have tested positive. The team has sampled several dozen households across the county so far (about the project, visit http://tx.ag/BCSCovidResearch; Promed archive number : 20200808.7658191).
- **Dog (North Carolina, USA)**
  A North Carolina dog supposedly died from COVID-19 complications the week of 3rd August 2020 said state health officials however there is little information about the dog and if there were underlying factors in the death of this animal (ProMed archive number : 20200813.7672505). The dog's owner took it to a veterinary hospital, reporting breathing problems, and told staff it had earlier tested positive for SARS-CoV-2 and recovered. A test for the dog came back positive at the vet's office.

The majority of the confirmed domestic animal cases are strongly linked to a confirmed existing human infection, and there is no evidence of animal to animal transmission in companion animal settings. This suggests human to animal transmission is the primary mode of spread in domestic settings. Viral load, route of infection, national and international context and age of pets may influence transmission probability (Shi , manuscript on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.03.30.015347v1).

There is currently no evidence that cats or dogs play a significant role in human exposure; however, reverse zoonosis is possible if infected owners expose their domestic pets during acute infection (Bosco-Lauth, manuscript on Biorxiv: https://doi.org/10.1101/2020.05.28.120998). Detection of SARS-CoV-2 infections in domestic animals has raised some

concern that there may be an increase in the number of people leaving their pets (Gönültaş 2020, see ***below***). Computer simulations have been performed to estimate how this may affect outbreak related outcomes. Abandonment of animals may result in significant differences in the risk of transmission (Gönültaş 2020, see ***below***; Gao 2020, see ***below***).

As of August 15, it is debated that dogs have died of COVID19 without *post-mortem* examination with ancillary diagnostics, and a clear history of the health status of the dead animals (ProMed archive Number: 20200815.7681907). The factual information gained from a *post-mortem* examination can then benefit the veterinary community and pet owners. It thus seems premature and inappropriate to make claims that dogs (NC dog and NY German shepherd) are dying of COVID-19 as coronavirus infection and coronavirus disease should not be considered synonymous and differential diagnosis should be systematically carried out (e.g. for canine coronavirus infection (CCV)). Only then can such statements like "...dog died from coronavirus [COVID-19] complications..." actually be verified. Until this happens, these statements continue to create confusion and panic in the population. An animal specific RT-PCR test has been developed by IDEXX Reference Laboratories to detect SARS-CoV-2 based on the published genetic sequences of the virus from the human outbreak. The test targets the same nucleocapsid gene as the CDC assay but has been adapted with a unique alignment for use in animals. As such it is designed to avoid cross-reactivity with other veterinary-specific coronaviruses (Promed archive number: 20200818.7689234).

The CDC are recommending that people treat pets as they would other human family members and to not let them interact with people or animals outside the household. It also recommended that if someone in the family develops symptoms, they also be isolated from pets (https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/pets.html). A possible role of cats in the epidemiology of COVID-19 is yet to be further studied. Akhmetzhanov (manuscript on MedRvix: https://www.medrxiv.oreg/content/10.1101/2020.05.21.20109041v1) reviewed 17 case reports on confirmed SARS-CoV-2 infections in animals as of 15 May 2020 and estimated the basic reproduction number R0 under a scenario of cat-to-cat transmission at 1.09 (95% confidence interval: 1.05, 1.13). This value is much lower than the R0 reported for humans and close to one, suggesting that the sustained transmission between cats is unlikely to occur. Bosco-Lauth (manuscript on bioRxiv : https://doi.org/10.1101/2020.05.28.120998) found that cats are highly susceptible to subclinical infection, with oral and nasal viral shedding that is not accompanied by clinical signs, and are capable of direct contact transmission to other cats. Dogs do not shed virus following infection. Cats and dogs developed a robust neutralizing antibody response indicative of established protective immunity against SARS-CoV-2 following repeated exposure. Despite early reports of possible mink-to-human transmission in the Netherlands, there is currently no peer reviewed evidence that animals contribute to the transmission of SARS-CoV-2 within human populations.

Zoo animals

Five tigers and three lions at the Wildlife Conservation Society's (WCS) Bronx Zoo in New York have tested positive for SARS-CoV-2. (ProMED-mail, Archive Number: 20200406.7191352., https://promedmail.org/promed-post/?id=20200406.7191352; ProMED-mail, Archive Number: 20200406.7191480., https://promedmail.org/promed-post/?id=20200406.7191480; OIE WAHID, https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=34054; Wildlife Conservation Society, https://newsroom.wcs.org/News-Releases/articleType/ArticleView/articleId/14084/Update-Bronx-Zoo-Tigers-and-Lions-Recovering-from-COVID-19.aspx).

All five tigers and three lions were housed in two enclosures at the zoo, which had been closed to the public since mid-March. Initially, the OIE WAHID received a report on 6th April that COVID-19 was confirmed in one of the Malayan tigers (*Panthera tigris jacksoni*) that developed mild clinical signs of respiratory disease (dry cough and some wheezing)

on the 27th March. Duplicate nasal and oropharyngeal swabs and tracheal wash samples were collected and confirmed to be positive for SARS-CoV-2 by RT-PCR and sequencing on 4th April.

By 3rd April, three additional tigers (one additional Malayan tiger and two Amur tigers) and all three African lions were also showing the same clinical respiratory signs as the index case, with anorexia also reported in one or more animals (no further details provided). No dyspnoea, or ocular or nasal discharge were observed in any of the cats.

These tigers and lions were not initially tested due to logistical challenges, but were assumed to also be infected with SARS-CoV-2. All animals in the two affected enclosures were isolated, and symptomatic animals were administered antibiotics and/or supportive care as needed. They reportedly showed daily improvement of clinical signs and appeared to be recovering well. A subsequent notification to the OIE on 17th April reported confirmation of SARS-CoV-2 infection in one of the lions, and reportedly also in all five other suspected animals, via a faecal test. An 8th case in an in-contact tiger with no clinical signs was also detected. No further details were provided regarding the test performed. All the large cats were reported to be recovering well.

Transmission is presumed to have occurred from a pre- or asymptomatic animal keeper infected with SARS-CoV-2, but no confirmed staff infections have been reported to date. It is also not confirmed whether all the animals were infected at the same time by the presumed infected keeper, or whether the first tiger to show clinical signs subsequently transmitted the virus to the other animals. As of October 20 2020, the source of SARS-CoV-2 infection in the lions remains unknown. Epidemiological data and genetic similarities between keeper and tiger viruses indicate human to animal transmission (McAloose, 2020 mBio : see ***below***). An in-depth review of this case series provided a detailed description of the the clinical presentation, diagnostic evaluation, and management of tigers and lions infected with SARS-CoV-2 (Bartlett, manuscript on bioRxiv : https://www.biorxiv.org/content/10.1101/2020.08.14.250928v1). A second case study of this series presented the first known natural transmission of SARS-CoV-2 from humans to animals in the USA, the results of radiography and ultrasonography, viral shedding and samples positivity (oropharyngeal, nasal swabs, tracheal wash fluid, faecal) and provided the first report of SARS-CoV-2 in non-domestic felids.

On August 12, OIE received the notification of the Department of Agriculture, Forestry and Fisheries, Animal Production and Health, Pretoria, in South Africa that a zoo puma (*Felis concolor*) in Johannesburg's zoo (Gauteng) had tested positive for SARS-CoV-2. Disease symptoms appeared on 17th July with quarantine of the infected animal ; testing of the 2nd puma that was in direct contact with the case will be repeated in the following weeks (ProMed archive number : 20200813.7672007). On 31st July, the PCR test carried out by the University of Pretoria - Virology Laboratory (Private Laboratory) confirmed that the animal was positive for SARS-COV-2. The transmission is presumed to have occurred after contact with an infected handler as in the New York scenario (https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?page_refer=MapFullEventReport&reportid=35399).

None of the other big cat species, including snow leopard, cheetah, clouded leopard, Amur leopard or serval, nor other animals at the zoo have shown any signs of respiratory disease.

Sanctuaries and protected areas

Non-human primates

On 13th March 2020, the International Primate Society together with the UICN Primates SG strongly recommended that great ape visitations by humans are reduced to the minimum needed to ensure the safety and health monitoring for the non-human primates. For those essential staff, great ape visitation rules need to be strictly enforced at all sites (maintenance of a 10 meters distance from great apes at all times; moreover, no clinically ill person or who has been in contact with anybody ill in the preceding 14 days is allowed to visit great apes). While there has been no report of

SARS-CoV-2 infection in wildlife sanctuaries so far, it is safest to assume that great apes are susceptible to SARS-CoV-2 infection (Melin, manuscript on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.04.09.034967v2). Patrono (Em Micr Inf 2020, see ***below***) reported a mild respiratory outbreak of βCoV 1 (HCov-OC43) in habituated Tai forest chimpanzees in Cote d'Ivoire. Viral RNA was found in faeces of chimpanzees. The virus was probably introduced by asymptomatic visitors whose throat swabs tested positive for the virus.

Wild cats

On 4th April 2020, a wild tiger of the Pench Tiger Reserve area in Madhya Pradesh and Maharashtra, India, died after exhibiting altered behaviours and high fever. This area is considered one of the critical tiger habitats remaining in central India, hosting a population of around 44 tigers. Based on the confirmation of SARS-CoV-2 infections in captive tigers in the USA, all forest department officials of Pench Tiger Reserve were immediately quarantined in the forest and the reserve was closed to visitors. Veterinary authorities subsequently reported that an impacted intestine had caused the tiger's death; no details were provided about whether testing for SARS-CoV-2 was conducted. (https://www.freepressjournal.in/bhopal/madhya-pradesh-pench-forest-staff-qurantined-after-death-of-corona-positive-tiger-is-fit-now; https://www.nytimes.com/2020/04/22/science/india-tigers-coronavirus.html).

Mink farms

On April 26th, the Ministry of Agriculture of The Netherlands confirmed that two mink farms reported cases of COVID-19 among their animals (https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/OIE_SARS_CoV%202_infection_of_mink_in_the_Netherlands_26April2020.pdf). Minks showed various symptoms including respiratory problems, pneumonia, gastrointestinal problems and increased mortality (OIE statement, 28th April, https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/6th_call_OIE_AHG_COVID19_and_animals.pdf). An investigation by Utrecht University (UU), GD Animal Health, Erasmus MC and Wageningen Bioveterinary Research (WBVR) has been launched to determine the source of the infections, to better understand the epidemiology and allow for a better risk assessment. Authorities assumed that employees with COVID-19 symptoms infected the minks. Some employees at each of the farms had reportedly shown signs consistent with COVID-19 infection, however no details of testing in humans were provided at the time. It was later reported that at least one employee on each of the two farms had tested positive for SARS-CoV-2 (Oreshkova, manuscript on bioRxiv: https://www.biorxiv.org/content/biorxiv/early/2020/05/18/2020.05.18.101493.full.pdf).

As of 8th May, three additional mink farms tested positive for the virus; in these farms, contamination from humans to animals is presumed to be the cause. The government immediately established a 400m buffer zone around the affected farms, closed the nearest public roads, banned transport of animals and manure from the infected farms and requested other mink farm employees and veterinarians to notify any clinical signs resembling of COVID-19 in mink.

Follow-up testing showed that virus was found in the air samples outside the immediate vicinity of minks on dust particles within the house. It is still unknown whether people can become infected with COVID-19 through these dust particles, but personal protective equipment has been recommended for all employees at infected mink farms (Statement of Dutch Minister of Agriculture, Nature and Food Quality (LNV), 8th May 2020; https://www.rijksoverheid.nl/ministeries/ministerie-van-landbouw-natuur-en-voedselkwaliteit/nieuws/2020/05/08/eerste-resultaten-onderzoek-naar-covid-19-op-nertsenbedrijven-binnen).
Virus was not detected in dust or air samples taken from outside the buildings, meaning the risk to public health was negligible; consequently, the 400-metre closure zones around infected farms were cancelled by the Dutch Agriculture Minister as of 15th May (Statement of Dutch Minister of Agriculture, Nature and Food Quality (LNV), 15th May 2020, https://www.tweedekamer.nl/kamerstukken/brieven_regering/detail?id=2020Z08824&did=2020D18884).

Serological investigations of cats living on the mink farms identified antibodies against SARS-CoV-2 in 7/24 cats tested on the first farm, and virus was isolated from one of the seven positives, although in insufficient quantities to allow genetic sequencing. While it is not yet possible to determine how or when the cats became infected, or what their role may have been in transmission, the possibility of mink-to-cat transmission is being considered (Joint Statement of Dutch Ministers of Health, Welfare and Sport (VWS) and Agriculture, Nature and Food Quality (LNV), 25th May 2020; https://www.rijksoverheid.nl/regering/bewindspersonen/carola-schouten/documenten/kamerstukken/2020/05/25/kamerbrief-ontwikkelingen-covid-19-op-nertsenbedrijven).

Whether SARS-COV-2 can be transmitted from mink-to-mink is still debated but a preprint paper discusses minks as a potential SARS-CoV-2 reservoir due to similar infectivity patterns to bats (Guo, manuscript on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.01.21.914044v2.full). Further concerns have been raised linked to potential transmission from cage to cage, the breeding seasonality of minks (March-May), increased mink density (5 mink kits/female) as high densities of a species that has proven to be permissive to SARS-CoV-2 replication is a likely scenario that might increase mink-to-mink and mink-to-human transmission risk (ProMED-mail, Archive Number: 20200511.7323845, https://promedmail.org/promed-post/?id=20200511.7323845).

In an update on 19th May, Minister Schouten declared infection of mink with SARS-CoV-2 on mink farms to be an infectious animal disease according to the Animal Health and Welfare Act, after genetic sequencing of viral samples from employees and animals on the farms indicated a "plausible" case of mink-to-human infection (Statement of Dutch Minister of Agriculture, Nature and Food Quality (LNV), 19th May 2020; https://www.rijksoverheid.nl/documenten/brieven/2020/05/19/stand-van-zaken-onderzoek-covid-19-naar-nertsenbedrijven). The employee, who has since recovered, had worked with the mink before the farm was known to be infected, and prior to the implementation of employee personal protective equipment. At least one more potential occurrence of mink-to-human transmission was also reported on a second infected farm on 25th May, after genetic sequencing of viral samples from three infected humans revealed high homology of the viral strains with those in the farm's infected mink, and the absence of similar SARS-CoV-2 strains in other people in the region or in the environment (Joint Statement of Dutch Ministers of Health, Welfare and Sport (VWS) and Agriculture, Nature and Food Quality (LNV), 25th May 2020; https://www.rijksoverheid.nl/regering/bewindspersonen/carola-schouten/documenten/kamerstukken/2020/05/25/kamerbrief-ontwikkelingen-covid-19-op-nertsenbedrijven)

Given the rapidly evolving situation, and the fact that sub-clinically infected mink could see infected farms remaining "under the radar", mandatory weekly submission of all naturally dead mink for PCR testing ("early warning") and one-off serological screening of all mink farms in the country was implemented from 20th May. Visitors to infected farms have been banned, and owners are advised to prevent cats from entering or leaving company premises due to their susceptibility to infection with SARS-CoV-2 and potential role in viral transmission on farm premises. The role of cats in the spread of SARS-CoV-2 within and between mink farms in the Netherlands is currently under investigation. It will be of particular interest to note if such spread could involve the faecal route (Promed archive number: 20200617.7480013). By 15th June, the weekly carcass testing of naturally dead mink had detected SARS-CoV-2 infection in an additional ten farms, bringing the country's total number of infected mink farms to 15. In a letter to parliament dated 3rd June it was announced that in the interest of public health, all mink on the infected farms are to be culled within the following week (Joint Statement of Dutch Ministers of Health, Welfare and Sport (VWS) and Agriculture, Nature and Food Quality (LNV), 3rd June 2020; https://www.rijksoverheid.nl/onderwerpen/coronavirus-covid-19/documenten/kamerstukken/2020/06/03/kamerbrief-over-aanvullende-maatregelen-voor-nertsenbedrijven). The presence of peak numbers of mink kits on the farms at present and their decreasing maternal antibody protection over time will increase the number of susceptible animals on-farm by five to six times. This would pose the risk of uncontrolled viral transmission between mink and the potential for viral mutation and reassortment, as well as the establishment of a viral reservoir that could continue to re-infect humans. Infected farms will be required

to be cleaned and disinfected following the cull, and must remain empty for a period of time. Owners will be compensated for the loss of their animals. The uninfected mink farms are still required to continue the 'early warning' and screening activities described earlier. On 30th July, a total of 27 mink farms in the Netherlands have been declared infected and all 26 previously infected farms, in which SARS-CoV-2 was established, have been culled (Promed archive Number: 20200727.7617582 and 20200801.7635820). As of 17th August, SARS-CoV-2 had been found on 33 mink farms, and ±1.5 million mink had been culled because of SARS-CoV-2, representing some 30% of the animals kept on the country's 128 mink farms (Promed archive number: 20200817.7687830). By September 25 2020, the number of infected mink farms reached 57 in the Netherlands, and it went up to 64 by October 12 (Promed archive number: 20201013.7858915). Despite the tightening of control measures, the infection of distant farms raises further concerns on the pathways and mechanism of continued circulation and spread of the virus (Promed archive numbers : 20200909.7761598, 20200914.7777661, 20200918.7794239, 20200925.7813579). In the framework of these investigations, 1000 blood samples from 500 dogs, 500 cats and rabbits (number unknown) were examined. Antibodies against SARS-CoV-2 have been detected in 2 of the 500 cats (0.4%), one of the 500 dogs (0.2%), but not in rabbits. The prevalence within this tested population was thus found low, indicating that infections in cats and dogs are occasional, probably due to human spread.

In 2015, mink farming was banned in the Netherlands, but the ban was said to become fully effective in 2024 (https://www.eurogroupforanimals.org/news/dutch-court-confirms-ban-mink-farming-netherlands) even though pressure is mounting on the government to order a preventative cull across the entire sector now especially since mink are known to have passed the virus on to at least 2 farm workers (Promed archive number: 20200817.7687830). The world's largest fur production is located in China, and minks have been mentioned in China among the animal species addressed as potential intermediate hosts of COVID-19 (Guo, manuscript on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.01.21.914044v4). Following these developments, the Chinese agriculture ministry is considering rebranding minks (and other wildlife such as raccoon dogs, silver foxes and blue foxes) – that were also sold at Wuhan market - as domestic livestock, rather than wild animals, lobbying welfare and sanitary standards will be improved while protecting the fur farming business (ProMED-mail, Archive Number: 20200511.7323845, https://promedmail.org/promed-post/?id=20200512.7328587). As a consequence of the SARS-CoV-2 widespread infection in mink farms in the Netherlands, more than 100 mink farms will be ordered to close earlier than 2024. According to the Dutch Federation of Pelt Farmers, the Netherlands exports around 90 million euros [USD 101 million] worth of fur a year for use in China and globally. The country had roughly 900 000 mink at 130 farms (Promed archive number : 20200830.7730463).

A first in-depth investigation of outbreaks on 16 mink farms and humans living or working on these farms, using whole-genome sequencing (sequences available on GISAID: www.gisaid.org/) examined how SARS-CoV-2 was initially introduced from humans and evolved, most likely reflecting widespread circulation among mink in the beginning of the infection period several weeks prior to detection. The report also documented the first reverse spillover transmission events – that is animal-to-human transmissions - of SARS-CoV-2 from mink to people (Oude Munnink, manuscript on bioRxiv : https://doi.org/10.1101/2020.09.01.277152). In total, 18 sequences from mink farm employees or close contacts were generated from seven different farms. In most cases, these human sequences were near-identical to the mink sequences from the same farm. For two farms, the human sequences clustered deeply within the sequences derived from mink, with 7 nucleotides and 4 nucleotides difference with the closest related mink sequence. Moreover, sequences of employees sampled at a mink farm clustered with animals from another farm which can be explained by the exchange of personnel between these two farms. As of September 2, 2020, despite enhanced biosecurity, early warning surveillance, and immediate culling of infected farms, there was ongoing transmission between mink farms with 3 big transmission clusters with unknown modes of transmission. This exhaustive paper relating the One Health investigation outbreak team efforts to understand the epidemiology of SARS-

CoV-2 in mink farms was based upon data collected up to 26 Jun 2020 from 16 mink farms; as of September 2 2020, 28 additional farms have been found infected.

On June 17th, the Danish Veterinary and Food Authority issued a press release to advise that SARS-CoV-2 had been confirmed on a mink farm in the North Jutland region (press release of the Danish Veterinary and Food authority, https://www.foedevarestyrelsen.dk/Nyheder/Aktuelt/Sider/Pressemeddelelser%202020/Covid-19-i-nordjysk-minkbes%C3%A6tning.aspx); a dog from this household was tested positive for COVID-19 and isolated indoors with its owners (Promed Archive Numer : https://promedmail.org/promed-post/?id=7506728). Samples from 34 mink were tested after a person who was associated with the farm was diagnosed with COVID-19. Entry and egress restrictions were placed on the mink farm while testing was being completed, and normal hygiene protocols for visitors to mink farms (including washing hands and changing clothes before and after animal handling) are still in force. The Danish government decreed that the infected farm will be depopulated in the interest of public health, and strategies for testing other mink farms in the country are reportedly being drawn up. As of July 5th, mink holdings infected with SARS-CoV-2 are no longer culled in Denmark. That is the decision of the Agriculture Ministry in Copenhagen. Based on a new strategy, a series of preventive measures are being pursued, such as the obligation to use protective equipment on farms and the promulgation of hygiene guidelines. A council's order will come into effect in the course of this month [July 2020] (Promed Archive Number: 20200708.7553067). The Danish Veterinary and Food Administration is currently testing all Danish mink farms for COVID-19 which led to detection on 14 Aug 2020, of a 4th infected farm (Promed archive number: 20200817.7687830). Since September 16, the DVFA no longer issues press releases on individual findings of COVID-19 on Danish mink farms. Instead, herds with confirmed infections are identified on the DVFA's website in a continuously updated map and table. In total, as of 18th and 25th September, 20 and 25 mink holdings respectively have been found COVID-19 infected out of the country's total of 1136 holdings (Promed archive number: 20200918.7794239, Promed archive number: 20200925.7813579). Since September 11, the Danish Veterinary and Food Administration (DVFA) has monitored Denmark's 1136 mink farms for the presence of the COVID-19 and identified 6 positive mink farms. With a monitoring strategy and the stricter restrictions for infected mink farms, the DVFA and the Danish health authorities assess that it is justifiable to let infected herds live because they consider that the risk of spreading infection to humans is minimal (Promed archive number: 20200914.7777661). However, this policy has apparently changed (https://www.oie.int/fileadmin/Home/MM/Update_4_Letter_to_OIE_on_Sars-CoV-2_in_mink_farms_in_Denmark.pdf). As of October 4th 2020, an increase in infected mink farms was noted, with 41 confirmed and 20 suspected farms. By October 14 2020, the number had risen to 89 (Promed archive number: 20201004.7835635 and 20201014.7861560). The Danish Ministry of Environment and Food stated that as many as one million mink will have to be culled (Promed archive number: 20201004.7835635). Interestingly, 1500 Danish fur farmers produce approx. 19 million mink skins; Denmark is a global hub for the mink fur trade, sells the 19 million Danish mink skins and around 7 million mink skins from other countries annually; China being its largest market.

On July 17th 2020, Spanish health authorities ordered the culling of all 93 000 mink at a farm in eastern Spain to prevent human contagion after discovering that most of the animals had been infected with the coronavirus where the owner had previously tested positive (May 20202). The farm is located in the village of La Puebla de Valverde in the region of Aragon, 200 km (125 miles) east of Madrid. Authorities initially ordered that the animals should be isolated. But a few weeks later, after several rounds of testing, they decided to cull the mink, which are farmed for their fur. As many as 80% of a sample of the animals tested positive.

On August 17th, the USA Department of Agriculture (USDA) reported the two first cases of mink fur farms in Utah to have tested positive for SARS-CoV-2. A state agriculture laboratory in Utah performed necropsies on several minks after "unusually large numbers of mink died at the farms," the USDA said. A Washington State University lab found that samples of 5 animals were positive for the virus, and the USDA's veterinary lab confirmed the results. The two farms have been quarantined, and there are no immediate plans for culling (Promed archive number:

20200818.7692815). The USDA-APHIS, United States Department of Agriculture, Washington, United States of America reported a third infected mink farm to the OIE on August 27, 2020. (https://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?reportid=35525). Following increased mortality rates (from 10.26% to 41.99%), domestic American Mink (*Neovison vison*) from three commercial premises were confirmed positive for SARS-CoV-2 at the National Veterinary Services Laboratories based upon molecular testing (PCR and sequencing). Clinical signs included respiratory signs and sudden death. State Officials in Utah have quarantined the premises and are working closely with federal One Health partners to complete disposal and monitor the situation.

By October 19 2020, thousands of minks at Utah fur farms in the USA had died because of SARS-CoV-2 infection in the preceding 10 days, forcing 9 sites in 3 counties to quarantine. The exact number of infected farms was not known. (Promed archive number : 20201009.7847704). Between 7000 and 8000 minks have died since the disease swept through the ranches producing the animals. No animals in Utah have been euthanized because of the disease : according to the Utah chief veterinarian, such measure did not appear to be necessary. Fur from the dead infected animals will be processed to remove any traces of the virus and then used for coats and other garments, according to Fur Commission USA, a mink farming trade group. The US produces more than 3 million mink pelts each year. It is interesting to compare how the USA, as compared to the Netherlands, Spain, and Denmark, are tackling this issue. As of October 20 2020, only the USA seem to consider the culling of infected mink unnecessary.

Human populations at risk

Early publications provided preliminary analyses of the main risk factors of COVID-19. For instance, a retrospective, single-centre study, including all confirmed cases of COVID-19 in Wuhan Jinyintan Hospital from Jan 1 to Jan 20, 2020 described 99 patients with PCR-confirmed COVID-19 pneumonia (Chen Lancet 2020, see ***below***). Forty-nine (49%) had a history of exposure to the Huanan seafood market. The average age of the patients was 55.5 years (SD 13.1), including 67 men and 32 women. Fifty (51%) patients had chronic diseases. In this study, the disease was found more likely to affect older males with comorbidities.

Guan (Eur Respir J 2020, see ***below***) analysed the data from 1590 laboratory-confirmed hospitalised patients 575 hospitals in 31 province/autonomous regions/provincial municipalities across mainland China between December 11th 2019 and January 31st 2020. The mean age of patients was 48.9 years. 686 patients (42.7%) were females. Severe cases accounted for 16.0% of the study population. 131 (8.2%) patients reached to the composite endpoints. 399 (25.1%) reported having at least one comorbidity. The most prevalent comorbidity was hypertension (16.9%), followed by diabetes (8.2%). 130 (8.2%) patients reported having two or more comorbidities. After adjusting for age and smoking status, COPD [hazards ratio (HR) 2.681, 95% confidence interval (95%CI) 1.424-5.048], diabetes (HR 1.59, 95%CI 1.03-2.45), hypertension (HR 1.58, 95%CI 1.07-2.32) and malignancy (HR 3.50, 95%CI 1.60-7.64) were risk factors of reaching to the composite endpoints. The HR was 1.79 (95%CI 1.16-2.77) among patients with at least one comorbidity and 2.59 (95%CI 1.61-4.17) among patients with two or more comorbidities.

Similarly, a meta-analysis by Wang (Aging 2020, see ***below***) analysed six studies from China, including 324 severe cases and 1234 non-severe cases, which provided data in terms of hypertension, diabetes, and COPD. Hypertension, diabetes, COPD, cardiovascular disease, and cerebrovascular disease were found to be major risk factors for patients with COVID-19. The meta-analysis revealed no correlation between increased risk of COVID-19 and liver disease, malignancy, or renal disease.

Epidemiological data were also reported from other countries. For instance, a report of the Korean Society of Infectious Diseases; Korean Society of Pediatric Infectious Diseases; Korean Society of Epidemiology; Korean Society for Antimicrobial Therapy; Korean Society for Healthcare-associated Infection Control and Prevention; and Korea

Centers for Disease Control and Prevention (J Korean Med Sci 2020, see ***below***) described the key epidemiological features of the disease in Korea.

Jordan (BMJ 2020, see ***below***) provided a quick overview of previously reported observations that older age, cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer were all associated with an increased risk of death. A meta-analysis of eight studies including 46 248 patients with laboratory confirmed covid-19 indicated that those with the most severe disease were more likely to have hypertension (odds ratio 2.36 (95% confidence interval 1.46 to 3.83)), respiratory disease (2.46 (1.76 to 3.44)), and cardiovascular disease (3.42 (1.88 to 6.22)). In other studies, obesity and smoking were associated with increased risks. However, the authors noted that the relative importance of different underlying health conditions remains unclear, owing to inadequate adjustment for important confounding factors such as age, sex, and smoking status; insufficient follow-up; and likely under-reporting of pre-existing conditions. In China, health records are often incomplete or inaccurate and chronic conditions are underdiagnosed.

Risk factors

A retrospective study involving COVID-19 cases reported through February 11, 2020, and corresponding to 72 314 patient records including 44 672 (61.8%) confirmed cases, was reported by the Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (Zhonghua Liu Xing Bing Xue Za Zhi 2020, see ***below***; and Wu JAMA 2020, see ***below***). Among confirmed cases, most were aged 30-79 years (86.6%), diagnosed in Hubei (74.7%). The male-to-female ratio was 0.99:1 in Wuhan, 1.04:1 in Hubei, and 1.06:1 in China overall.

Yang (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.28.20028068v1), who analysed 55 consecutive cases in Beijing, also showed that compared with patients without pneumonia, those with pneumonia were 15 years older and had a higher rate of hypertension.

The characteristics of patients may also at least in part reflect the movement and the social activities of individuals in different societies (Korean Society of Infectious Diseases J Korean Med Sci 2020, see ***below***). In the Korean situation, for instance, a predominance of females and subjects in their 20s among COVID-19 cases may be due to the fact that the outbreak related to a religious group.

Age

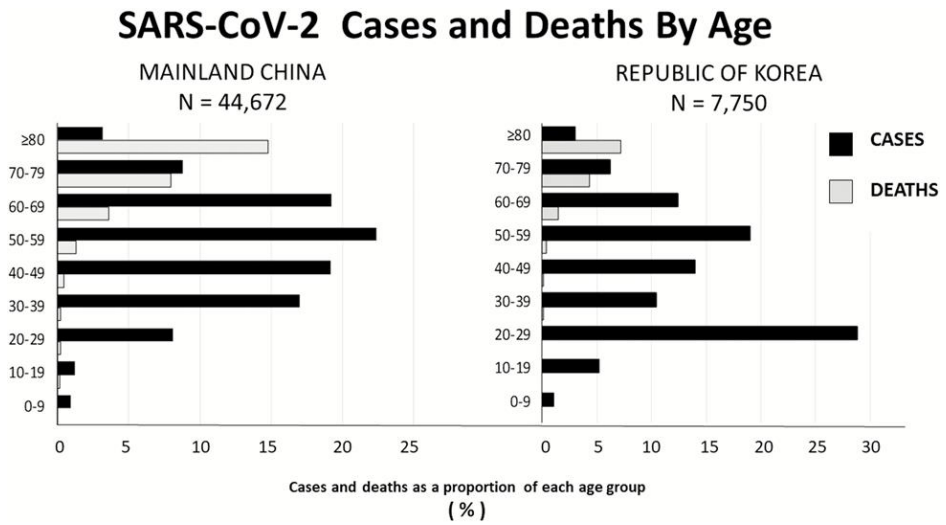
Early studies identified age as a major risk factor for COVID-19. ***Table 5*** presented above, showed the risk of infection according to age as detected in the analysis of 72 314 patient records in China. Multiple reports described the same risks factors leading to severe disease and death as those identified as disease risk factors. Wang (J Med Virol 2020, see ***below***) reported the details of the first 17 deaths up to 24:00 pm 22 Jan 2020. The deaths included 13 males and 4 females. The median age of the deaths was 75 (range 48-89) years. The median days from first symptom to death were 14.0 (range 6-41) days, and tended to be shorter among people 70 years of age and above (11.5 [range 6-19] days) than those with ages below 70 years (20 [range 10-41] days, P=0.033).

Dudley (Clin Inf Dis 2020, see ***below***), based on available data as of Feb 11 and March 11 respectively, compared the incidence of the disease and related deaths in China and South Korea according to age (***Figure 15***). Unexpectedly, a bimodal distribution of disease cases was observed in Korea, with highest morbidity in the 20-29 years cohort.

Of note, available studies usually considered chronological age as a risk factor. As highlighted by Lauc (Aging 2020, see ***below***), a number of biomarkers aimed at objective estimation of biological age have been developed in the past several years, the most prominent ones being the epigenetic clock and the glycan clock. The repertoire of glycans changes with age, especially in the age ranges that are most susceptible to SARS-CoV-2. Furthermore, both SARS-CoV-2 and its target ACE2 are known to be highly glycosylated, a pattern that likely changes with age. Recent study analysed site-specific N-linked glycosylation of MERS and SARS S glycoproteins, indicating that each of these glycosylation sites

can be occupied by up to ten different glycans (called glycoforms), which greatly extends epitope diversity. The authors therefore recommended modern profiling technologies to be used to identify molecular risk factors of COVID-19.

Figure 15 Incidence of disease and related death per age group in China and South Korea (from Dudley Clin Inf Dis 2020)



In the cohort of 78 patients reported by Liu (Chin Med J 2020, see ***below***), the patients in the progression group were also older than those in the disease improvement/stabilization group (66 [51, 70] vs. 37 [32, 41] years, U = 4.932, P = 0.001). Chen (BMJ 2020, see ***below***) analysed the profile of 113 patients who died and 161 who recovered with a diagnosis of COVID-19 up to February 28. The median age of deceased patients (68 years) was significantly older than recovered patients (51 years). Similarly, Shi (Crit Care 2020, see ***below***) found age, occupation, hypertension ($p<0.001$ for the comparisons between mild and severe cases), gender and cardiovascular disease ($p<0.003$) as risk factors.

Zhang (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.26.20028191v1) presented the clinical characteristics of 82 death cases of laboratory-confirmed as SARS-CoV-2 infection in Wuhan. Most of these death cases were male (65.9%). More than half of dead patients were older than 60 years (80.5%) and the median age was 72.5 years. The bulk of death cases had comorbidity (76.8%), including hypertension (56.1%), heart disease (20.7%), diabetes (18.3%), cerebrovascular disease (12.2%), and cancer (7.3%).

The retrospective study involving 44 672 confirmed COVID-19 cases reported by the Novel Coronavirus Pneumonia Emergency Response Epidemiology Team in China (Zhonghua Liu Xing Bing Xue Za Zhi 2020, see ***below***; and Wu Jama 2020, see ***below***) described a proportion of 13.8% severe cases and 4.7% critical cases in their database. The study concluded that the ≥80 years age group had the highest case fatality rate of all age groups at 14.8%. Case fatality rate for males was 2.8% and for females was 1.7%. While patients who reported no comorbid conditions had a case fatality rate of 0.9%, patients with comorbid conditions had much higher rates - 10.5% for those with cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer.

In line with the observations made in China, Porcheddu (J Infect Dev Ctries 2020, see ***below***) observed that fatalities in Italy mostly occurred in the elderly with known comorbidities.

Gender

Evidence of sex differences in COVID-19 severity emerged in China, where hospital admissions and mortality were higher among males than females. In South Korea, where community testing was widespread, females represented ~60% of those testing positive for SARS-CoV-2, suggesting that females acquire infection, despite having a lower case fatality rate (CFR). In the United States, where testing was prioritized for people with symptomatic disease, the diagnosis rates were similar in males and females, but males had 1.5 times higher mortality. A male bias in COVID-19

mortality has been reported in 37 of the 38 countries that have provided sex-disaggregated data. A report by Scully (Nat Rev Imm 2020, see ***below***) showed that the average male CFR across 38 countries is 1.7 times higher than the average female CFR (P < 0.0001) (male CFR 7.3 (95% CI 5.4–9.2); female CFR 4.4 (95% CI 3.4–5.5)).

Occupational risks

As noted by Koh (Occup Med 2020, see ***below***), a significant proportion of cases related to occupational exposure. The first documented occupational groups at risk were persons working in seafood and wet animal wholesale markets in Wuhan. At the start of the outbreak, workers and visitors to the market comprised 55% of the 47 cases with onset before 1 January 2020, when the wholesale market was closed.

Health care workers (HCWs) were next recognized as another high-risk group to acquire this infection. In a case series of 138 patients treated in a Wuhan hospital, 40 patients (29% of cases) were HCWs. Among the affected HCWs, 31 (77.5%) worked on general wards, 7 (17.5%) in the emergency department, and 2 (5%) in the intensive care unit (ICU). In Singapore, among the first 25 locally transmitted cases, 17 cases (68%) were probably related to occupational exposure. They included staff in the tourism, retail and hospitality industry, transport and security workers, and construction workers. A number of reports also highlighted the risks associated with the virus in saliva, especially for dentists and healthcare professionals that perform aerosol-generating procedures (e.g. Peng Int J Oral Science 2020, see ***below***; Sabino-Silva Clin Oral Investig 2020, see ***below***).

A situation to monitor is that of vegetable packing facilities, slaughterhouses, meat plants and seafood production facilities - including onboard fish processing factories - globally. Outbreaks in meat-processing plants have been common features of the pandemic, with research by the London School of Hygiene and Tropical Medicine showing that after ships, workers' dormitories, and jails (Promed archive number : Archive Number: 20200618.7482347) - food-processing factories have been responsible for the biggest localised outbreaks (ProMed Archive Number : 20200621.7492011). After Germany's red flags on the issue (https://www.dw.com/en/germanys-meat-industry-under-fire-after-covid-19-outbreaks/a-53502751), on May 20, 25.4% (570/2244) of workers in a poultry facility in North Carolina, U.S.A. tested positive for COVID-19 ; the majority of whom were asymptomatic (ProMed Archive Number: 20200523.7370321). Since April 2020, at least 15 300 reported COVID-19-positive cases have been connected to meatpacking facilities in at least 192 plants in 32 U.S. states (Dyal 2020, see ***below***). On May 25 2020, a pork processing facility in the Netherlands reported 22.3% (147/657) prevalence of COVID-19 among workers (79 originating from Germany where outbreak had occurred earlier) which prompted the authorities to close the facility, quarantine the infected workers and conduct an extensive track and trace program (ProMed Archive Number: 20200527.7381561). On May 26, a poultry and pork meat processing facility in Brazil reported a prevalence of 6.6% COVID-19 positive workers; the same measures are taken to prevent further spread (ProMed Archive Number: 20200527.7381561). On June 6, Seattle-based American Seafoods confirmed that 92/126 crew onboard a fish production ship had tested positive for COVID-19 (Source: Alaska Public Media on ProMed Archive Number: 20200606.7434798). There has been no mention of testing the animal products. A pork processing plant in Belgium reported 67 COVID-19 infections on August 7 2020 (ProMed Archive number: 20200809.7659384) and a frozen meat packing plant in Argentina reported 18/50 workers infected on August 2 2020 (Promed archive number: 20200901.7737977), joining the string of outbreaks at abattoirs and meat processing facilities around the world). As SARS-COV-2 survival times on surfaces is still poorly described (see ***Virus in the environment*** below), there is a need for research and cautionary control measures in these facilities. The July 2020 outbreak in a seafood plant in Northern China with a suspected index case contaminated with imported frozen products from South America raised further concern about virus survival and transcontinental circulation in packaged food (ProMed archive number: 20200724.7606897) and concerns that contaminated food shipments could lead to new outbreaks (ProMed archive Number: 20200814.7676661). On August 12, it was reported that SARS-CoV-2 was found on the outer packaging of frozen seafood bought by 3 companies in Yantai, a port city in eastern Shandong province (ProMed archive number:

20200812.7669363). A hierarchy of safety measures and the use of face shields for work stations of 1 meter or less seem to be the way forward in facilities where working on a chain does not allow increasing social distance (ProMed Archive Number: 20200602.7417630). However, a risk factor in such premises might be the environment - besides close contacts - with colder temperatures and absence of natural light, hence UV, that may favour live virus survival (ProMed Archive Number: 20200621.7492011). The latter conditions could also allow for virus survival in extreme cold natural environment such as the Antarctica and North pole (Barbosa, manuscript on Preprints: https://www.preprints.org/manuscript/202008.0478/v1). Low-temperature environment (and storage conditions in refrigerators, cold rooms, or transport carriers for storage of fish before selling) are increasingly pointed at since the beginning of the COVID-19 pandemic as potentially extending virus survival times. New experimental evidence suggests that SARS-CoV-2 may be viable on frozen salmon for one week at 4°C (Dai, manuscript on bioRxiv : https://doi.org/10.1101/2020.09.06.284695). Such report highlights the need for all employers to carry out a COVID-19 risk assessment prior to reopening or enhancing the operations, with the objective to reduce workplace risk to the lowest reasonably practicable level by implementing preventative measures (e.g., https://www.gov.uk/guidance/working-safely-during-coronavirus-covid-19/factories-plants-and-warehouses#factories-1-1). The Codex Alimentarius Commission has adopted several practical guidelines on how to apply and implement best practices to ensure food hygiene (Codex General Principles of Food Hygiene, CXC 1- 1969), handle meats (Codex Code of Hygienic Practice for Meat, CXC 58 – 2005), and control viruses in foods (Guidelines for the Application of General Principles of Food Hygiene to the Control of Viruses in Food (CAC/GL 79-2012) and others can be consulted on the Codex website (OIE, 2020: https://www.oie.int/en/scientific-expertise/specific-information-and-recommendations/questions-and-answers-on-2019novel-coronavirus/). Specifically, coronaviruses are thermolabile, which means that they are susceptible to normal cooking temperatures (70°C). Therefore, as a general rule, the consumption of raw or undercooked animal products should be avoided. Raw meat, raw milk or raw animal organs should be handled with care to avoid cross-contamination with uncooked foods. The WHO also issued a document entitled "COVID-19 and Food Safety: Guidance for competent authorities responsible for national food safety control systems" which aims to address how to ensure the effectiveness of a reduced food safety inspection programme in mitigation of risk, and temporary measures that can be introduced to contain widespread food safety risks (WHO, 2020: https://www.who.int/publications/i/item/covid-19-and-food-safety-guidance-for-competent-authorities-responsible-for-national-food-safety-control-systems).

Genetics

Delanghe (Clin Chim Acta 2020, see ***below***) postulated that the variability in deletion/insertion D/I ACE1 enzyme genotype distribution might partly explain the variable prevalence of the COVID-19 infection amongst continental European countries. ACE1 is indeed characterized by a genetic (D/I) polymorphism in intron 16, which is associated with alterations in circulating and tissue concentrations of ACE. This D/I polymorphism shows important geographical variation. The authors found that the log transformed prevalence of COVID-19 infections is inversely correlated with the D allele frequency: log (prevalence; number of cases/106 inhabitants) = 6.358–0.079 (D-allele frequency, %), r2 = 0.378; p = 0.001, which led to the conclusion that the ACE D/I genotype may affect the clinical course of the infection.

The first robust genetic susceptibility loci for the development of respiratory failure in COVID-19 were reported by Ellinghaus (manuscript on medRxiv, see https://www.medrxiv.org/content/10.1101/2020.05.31.20114991v1). The study involved 1,980 patients with COVID-19 respiratory failure (8,582,968 single-nucleotide polymorphisms), in a genome-wide association analysis. Cross-replicating associations with rs11385942 at chromosome 3p21.31 and rs657152 at 9q34, which were genome-wide significant. Among six genes at 3p21.31, SLC6A20 encodes a known interaction partner with ACE2. The association signal at 9q34 was located at the ABO blood group locus and a blood-group-specific analysis showed higher risk for A-positive individuals (OR=1.45, 95% CI, 1.20 to 1.75, P=1.48x10-4) and a protective effect for blood group O (OR=0.65, 95% CI, 0.53 to 0.79, P=1.06x10-5). Katz (manuscript on medRxiv, see https://www.medrxiv.org/content/10.1101/2020.06.09.20125690v1) further utilized proteomic profiling and genetic

information from three cohorts including black and white participants to identify proteins influenced by these loci. The authors observed that variants in the ABO locus are associated with levels of CD209/DC-SIGN, a known binding protein for SARS-CoV and other viruses, as well as multiple inflammatory and thrombotic proteins, while the 3p21.31 locus is associated with levels of CXCL16, a known inflammatory chemokine.

Recently, a review by Anastassopoulou (Hum Genomics 2020, see ***below***) provided an overview of human genetic factors associated with susceptibility to SARS-CoV-2 infection and COVID-19 disease severity (summarized in ***Table 10***).

Table 10. Summary of reported associations between human genes and COVID-19

Gene(s)	Polymorphism(s)	Chromosome location	Reported COVID-19 associations
ABO	rs657152	9q34.2	Higher risk of infection for blood group A vs. non-A (OR 1.45, 95% CI 1.20–1.75, $P = 1.48 \times 10^{-4}$) and lower risk of infection for blood group O vs. non-O (OR 0.65, 95% CI 0.53–0.79, $P = 1.06 \times 10^{-5}$)
ACE2	p.Arg514-Gly	Xp22.2	Cardiovascular and pulmonary conditions in the African/African-American population by altering AGT-ACE2 pathway
ApoE	rs429358-C-C (e4e4)	19q13.32	Severe disease independently of pre-existing dementia, cardiovascular disease, and type 2 diabetes
HLA	B*46:01 and B*15:03	6p21.33	Vulnerable to disease for *HLA-B*46:01* and cross-protective T cell-based immunity for *HLA-B*15:03*
IFITM3	rs12252-C/C	11p15.5	Mild-to-moderate disease requiring hospitalization
SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, XCR1	rs11385942-GA	3p21.31	Severe disease (respiratory failure) (OR 1.77, 95% CI 1.48–2.11, $P = 1.15 \times 10^{-10}$)
TLR7	g.12905756_12905759del and g.12906010G>T	Xp22.2	Severe disease
TMEM189-UBE2V1	rs6020298-A	20q13.13	Severe disease
TMPRSS2	p.Val160Met (rs12329760)	21q22.3	Increased susceptibility to disease and for risk factors, e.g., cancer

Smoking

Cai (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.05.20020107v3) observed significantly higher ACE2 gene expression in former smoker's lung compared to non-smoker's lung. Also, the authors found higher ACE2 gene expression in Asian current smokers compared to non-smokers, but not in Caucasian current smokers, which may indicate an existence of gene-smoking interaction. In addition, they found that ACE2 gene is expressed in specific cell types related to smoking history and location. In bronchial epithelium, ACE2 is actively expressed in goblet cells of current smokers and club cells of non-smokers. In alveoli, ACE2 is actively expressed in remodelled AT2 cells of former smokers. Leung (Eur Respir J 2020, see ***below***) demonstrated increased ACE2 expression in the small airway epithelia of current (but not former) smokers and those with COPD. These results are consistent with previous observations in small animals wherein smoke exposure has been shown to upregulate both the expression and activity of ACE2 in the airways. While the up-regulation of ACE2 may be useful in protecting the host against acute lung injury, chronically, this may predispose individuals to increased risk of coronavirus infections.

Based on a review of published data as of 17 March 2020, Vardavas (Tobacco Induced Diseases 2020, see ***below***) concluded that smoking is most likely associated with the negative progression and adverse outcomes of COVID-19. Indeed, the authors identified five studies reporting data on the smoking status of patients infected with COVID-19. Notably, in the largest study that assessed severity (Guan NEJM 2020, see ***below***), there were higher percentages of current and former smokers among patients that needed ICU support, mechanical ventilation or who had died, and a higher percentage of smokers among the severe cases. From these published data Vardavas calculated that the smokers were 1.4 times more likely (RR=1.4, 95% CI: 0.98–2.00) to have severe symptoms of COVID-19 and approximately 2.4 times more likely to be admitted to an ICU, need mechanical ventilation or die compared to non-smokers (RR=2.4, 95% CI: 1.43–4.04).

However, another review published in parallel by Lippi (Eur J Int Med 2020, see ***below***) reached different conclusions from the analysis of almost the same studies. The authors reported that in only one study (the study by Liu Chin Med

J 2020, see ***below***), active smoking was found to be a significant predictor of COVID-19 severity, whilst in the other four studies the association was not statistically significant.

Cai (Lancet Resp Med 2020, see ***below***) also considered that the relatively small proportion of current smokers in reported studies compared with the proportion of male smokers in China (50·5%) are unlikely to be associated with increased incidence or severity of COVID-19.

Moreover, a study by Shi (Crit Care 2020, see ***below***) based on 487 patients, not included in any of these 2 reviews, did not identify smoking as a risk factor.

A meta-analysis by Guo (J Med Virol 2020, see ***below***) was based on data from 8 trials, including a more recent study in 125 patients. The pooled OR of the fixed effect model was 2.16 (95% CI: 1.45-3.22). The study from Guan contributed to most of the cases in the meta-analysis (1 085 out of 1 851 cases). The sensitivity analysis excluding this study (that appeared as a major source of heterogeneity) revealed a pooled OR of 1.89 (95% CI: 1.10-3.24).

Alqahtani (PLoS One 2020, see ***below***) published a systematic review and meta-analysis on the potential severity and mortality risks caused by COVID-19 in patients with chronic obstructive pulmonary disease (COPD) and in smokers. A total of 15 studies, which included a total of 2473 confirmed COVID-19 patients were included in the meta-analysis. The crude case fatality rate of COVID-19 was 7.4%. The pooled prevalence rates of COPD patients and smokers in COVID-19 cases were 2% (95% CI, 1%-3%) and 9% (95% CI, 4%-14%) respectively. COPD patients were at a higher risk of more severe disease (risk of severity = 63%, (22/35) compared to patients without COPD 33.4% (409/1224) [calculated RR, 1.88 (95% CI, 1.4-2.4)]. This was associated with higher mortality (60%). The results showed that 22% (31/139) of current smokers and 46% (13/28) of ex-smokers had severe complications. The calculated RR showed that current smokers were 1.45 times more likely [95% CI: 1.03-2.04] to have severe complications compared to former and never smokers. Current smokers also had a higher mortality rate of 38.5%.

In June 2020, a meta-analysis of retrospective observational case series by Farsalinos (Ther Adv Chronic Dis 2020, see ***below***) found an unexpectedly low prevalence of current smoking among hospitalized patients with COVID-19. Hospitalized current smokers had higher odds compared with non-current smokers but lower odds compared with former smokers for an adverse outcome. Smoking cannot be considered a protective measure for COVID-19. However, the hypothesis that nicotine may have a protective effect in COVID-19 that is partially masked by smoking-related toxicity and by the abrupt cessation of nicotine intake when smokers are hospitalized should be explored in laboratory studies and clinical trials using pharmaceutical nicotine products.

Obesity

An editorial by Ryan (Obesity 2020, see ***below***) noted that persons with obesity around the world are already at high risk for severe complications of COVID-19, by virtue of the increased risk of the chronic diseases that obesity drives. The authors also consider likely that obesity shall be an independent risk factor for COVID-19.

A number of studies identified higher BMI as a risk factor for severe disease. For instance, at the beginning of the epidemic, Peng (Zhonghua Xin Xue Guan Bing Za Zhi 2020, see ***below***) conducted a retrospective analysis on 112 COVID-19 patients with cardiovascular disease in Wuhan, from January 20, 2020 to February 15, 2020. Patients were divided into critical group (ICU, n=16) and general group (n=96) according to the severity of the disease. The BMI of the critical group was significantly higher than that of the general group (25.5 (23.0, 27.5) kg/m(2) vs. 22.0 (20.0, 24.0) kg/m(2), P=0.003). Patients were further divided into non-survivor group (n=17) and survivor group (n=95). Among the non-survivors, there were 88.24% (15/17) patients with BMI> 25 kg/m(2), which was significantly higher than that of survivors (18.95% (18/95), P<0.001).

The analysis of the clinical characteristics, treatment and prognosis of 280 patients from four Chinese hospitals (from January 20 to February 19, 2020) by Wu (J Intern Med 2020, see ***below***) also found that the severe group had a significantly higher BMI values than the group of patients with mild disease (25.8 ± 1.8 vs. 23.6 ± 3.2, P = 0.005). However, a multifactor analysis revealed that other factors (comorbidity, time from illness onset to antiviral treatment, and age >=65) were independent risk factors for COVID-19 progression.

In the USA, among 6916 Kaiser Permanente Southern California members diagnosed with COVID-19 from 13 February to 2 May 2020, there was a J-shaped association between BMI and risk for death, even after adjustment for obesity-related comorbidities (Tartof Ann Int Med 2020, see ***below***). Compared with patients with a BMI of 18.5 to 24 kg/m2, those with BMIs of 40 to 44 kg/m2 and greater than 45 kg/m2 had relative risks of 2.68 (95% CI, 1.43 to 5.04) and 4.18 (CI, 2.12 to 8.26), respectively. This risk was most striking among those aged 60 years or younger and men. Of note, in this cohort, increased risk for death associated with Black or Latino race/ethnicity or other sociodemographic characteristics was not detected.

In Mexico, Giannouchos (Eur Respir J 2020, see ***below***) used a publicly available nation-level dataset released on May 31, 2020 by the Mexican Ministry of Health and examined the associations between patient characteristics and hospitalisation and adverse outcome. COVID-19 patients were found disproportionately older, males and with increased prevalence of one or more comorbidities, particularly diabetes, obesity, and hypertension. Age, male gender, diabetes, obesity and having one or more comorbidities were independently associated with laboratory-confirmed COVID-19. Male gender, older age, having one or more comorbidities, and chronic renal disease, diabetes, obesity, COPD, immunosuppression and hypertension were associated with hospitalisation and adverse outcome.

In England, Hamer (PNAS 2020, see ***below***) used data from a community-dwelling sample in England (n = 334,329; 56.4 ±8.1 y; 54.5% women) with prospective linkage to national registry on hospitalization for COVID-19. Around 0.2% (n = 640) of the sample were hospitalized for COVID-19. There was an upward linear trend in the likelihood of COVID-19 hospitalization with increasing BMI, that was evident in the overweight (odds ratio, 1.39; 95% CI 1.13 to 1.71; crude incidence 19.1 per 10,000) and obese stage I (1.70;1.34 to 2.16; 23.3 per 10,000) and stage II (3.38; 2.60 to 4.40; 42.7 per 10,000) compared to normal weight (12.5 per 10,000). This gradient was little affected after adjustment for a wide range of covariates; however, controlling for biomarkers, particularly high-density lipoprotein cholesterol and glycated hemoglobin, led to a greater degree of attenuation. A similar pattern of association emerged for waist-hip ratio. The authors suggested that mechanisms of impaired glucose and lipid metabolism may be involved.

More recently, a systematic review by Chang (Obes Rev 2020, see ***below***) examined the effects of BMI and obesity (BMI ≥ 30 kg/m2) on COVID-19. Sixteen articles were included in the meta-analysis, and a random effects model was used. BMI was found to be higher in patients with severe disease than in those with mild or moderate disease (MD 1.6, 95% CI, 0.8-2.4; p = .0002) in China; however, the heterogeneity was high (I2 = 75%). Elevated BMI was associated with invasive mechanical ventilation use (MD 4.1, 95% CI, 2.1-6.1; p < .0001) in Western countries, and this result was consistent across studies (I2 = 0%). Additionally, there were increased odds ratios of invasive mechanical ventilation use (OR 2.0, 95% CI, 1.4-2.9; p < .0001) and hospitalization (OR 1.4, 95% CI, 1.3-1.60; p < .00001) in patients with obesity. There was no substantial heterogeneity (I2 = 0%).

Diabetes

A meta-analysis of studies reporting the prevalence of diabetes among people infected with SARS-CoV-2 and its impact on disease severity or progression was reported by Fadini (J Endocrinol Invest 2020, see ***below***). 12 studies reporting data from 2108 Chinese patients with confirmed SARS-Cov-2 infection yielded an estimate of the prevalence of diabetes of 10.3%. For comparison, the nationwide prevalence of diabetes in China in 2013 was 10.9% overall and 12.3% among people aged 40–59. The authors concluded that diabetes may not increase the risk of SARS-CoV-2 infection, but can worsen the outcome of COVID-19.

Cardiovascular diseases

Results of a pooled analysis of the scientific literature (available as of March 26) by Lippi (Pol Arch Intern Med 2020, see ***below***) would suggest that hypertension may be associated with an up to 2.5-fold higher risk of severe and fatal COVID-19, especially among older individuals. A brief meta-analysis by Zuin (J Inf 2020, see ***below***) also demonstrated that patients with COVID-19 infection and hypertension have a significant high mortality risk.

Ruan (Intensive Care Med 2020, see ***below***) conducted a retrospective multicenter study of 68 death cases and 82 discharged cases with laboratory-confirmed infection. The authors found a significant difference in age between the death group and the discharge group ($p < 0.001$) but no difference in the sex ratio ($p = 0.43$). A total of 63% (43/68) of patients in the death group and 41% (34/82) in the discharge group had underlying diseases ($p = 0.0069$). Patients with cardiovascular diseases had a significantly increased risk of death when infected with SARS-CoV-2 ($p < 0.001$). A total of 16% (11/68) of the patients in the death group had secondary infections vs. 1% (1/82) of the patients in the discharge group ($p = 0.0018$).

Aggarwal (Curr Probl Cardiol 2020, see ***below***) conducted another meta-analysis of 18 recent studies that reported the association of cardio-vascular disease with worse prognosis and increased mortality in COVID-19 patients. Pre-existing cardiovascular disease was associated with a significantly increased risk of a severe form of COVID-19 (OR = 3.14; 95% CI 2.32-4.24; I2 = 0%; Q = 8.68, P= 0.73) and overall risk of COVID-19 all-cause mortality (OR = 11.08; 95% CI: 2.59-47.32; I2 = 55%; P = 0.11).

A meta-analysis by Krittanawong (Prog Cardiovasc Dis 2020, see ***below***) concluded that patients with pre-existing cardiovascular disease risk, such as diabetes mellitus and hypertension risk, as well as patients with established cardiovascular disease, are associated with a higher risk of developing severe COVID-19 disease.

Treatment with ACE inhibitors and angiotensin II type-I receptor blockers?

Wu (JAMA Int Med 2020, see ***below***) found that diabetes and hypertension to be more frequent in those who developed ARDS than those who did not. Fang (Lancet Resp Med 2020, see ***below***) noted that the most frequent comorbidities reported in studies of patients with COVID-19 are often treated with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type-I receptor blockers (ARBs) (even though treatment was not assessed in these published studies), which increase ACE2 expression. The authors therefore hypothesized that such treatment would increase the risk of developing severe and fatal COVID-19 in patients with cardiac diseases, hypertension, or diabetes. Diaz (J Travel Med 2020, see ***below***) developed a similar hypothesis. However, Patel (JAMA 2020, see ***below***) listed some arguments pointing to a very different view of the topic. For instance, there is limited evidence showing ACE2 expression increases in serum or lung after treatment with these drugs. Moreover, the significance of ACE2 expression on COVID-19 pathogenesis and mortality is not specifically known. And there are preclinical data suggesting that increasing ACE2 expression can attenuate SARS-CoV-2-induced lung injury. Cheng, Wang et al. (J Med Vir 2020, see ***below***) and Vaduganathan (NEJM 2020, see ***below***) provided similar arguments, and even suggested the possibility to treat ARDS with recombinant human ACE2 or ARBs. Meng (Em Micr Inf 2020, see ***below***) evaluated the ability of renin-angiotensin inhibitors to protect against COVID-19 in a small cohort of 42 patients with hypertension. The authors concluded in a protective effect of ACE inhibitors and ARBs on the severity of the disease. A study by Feng (Am J Respir Crit Care Med 2020, see ***below***), which included 476 patients, found a significant difference in ACE inhibitors/ARBs usage among patients with different disease severity. Compared with severe and critical groups, there were more patients taking ACE inhibitor/ARB in the moderate disease group. This observation may seem to confirm the data by Meng. However only few patients in this study used ACE inhibitor/ARB treatment (33/476), suggesting that more data are still required to draw firm conclusions on this topic.

Chronic kidney disease

Another meta-analysis by Henry (Int Urol Nephrol 2020, see ***below***) included four studies, corresponding to 1389 COVID-19 patients, among which 273 (19.7%) were classified as having severe disease. No study individually found chronic kidney disease as significant clinical predictor of severe COVID-19. However, when data of individual studies were pooled, a significant association of chronic kidney disease with severe COVID-19 was observed, with no relevant heterogeneity [OR 3.03 (95% CI 1.09–8.47), I2 = 0.0%, Cochran's Q, p = 0.84].

Cancer

Liang (Lancet Oncol 2020, see ***below***) described a retrospective analysis of cancer patients among 1590 COVID-19 cases. Eighteen (1%; 95% CI 0·61–1·65) of 1590 COVID-19 cases had a history of cancer, which seems to be higher than the incidence of cancer in the overall Chinese population (285·83 [0·29%] per 100 000 people, according to 2015 cancer epidemiology statistics). Lung cancer was the most frequent type (5/18 patients).

Similarly, Sidaway (Nature Rev Clin Oncol 2020, see ***below***) provided a short overview of the evidence available to document the link between cancer and COVID-19. While data remained limited, patients with cancer seem to be both more likely to be diagnosed with COVID-19 and have more severe symptoms.

From the analysis of a small cohort of 28 cancer patients, Zhang (Ann Oncol 2020, see ***below***) reported a case-fatality rate of COVID-19 reaching 28.6%.

Liang (Lancet Oncol 2020, see ***below***) reported that patients with cancer have a higher risk of severe events (a composite endpoint defined as the percentage of patients being admitted to the intensive care unit requiring invasive ventilation, or death) compared with patients without cancer (seven [39%] of 18 patients vs 124 [8%] of 1572 patients; Fisher's exact p=0·0003).

Other sources of risk

Following a cross-sectional study conducted in 3947 participants in Vietnam, Nguyen (J Clin Med 2020, see ***below***) reported that people with COVID-19 had a higher **depression** likelihood (OR, 2.88; p < 0.001) and lower Health Related Quality of Life-score (B, -7.92; p < 0.001).

Wise (BMJ 2020, see ***below***) reported a large UK study on **ethnic background** and risk of dying from COVID-19. Contrary to speculation, the higher risk of death in Asian and black ethnic backgrounds was only partly explained by comorbidity, deprivation, or other risk factors. The study found that black people had more than double the risk of dying from COVID-19 compared with those with ethnicity recorded as white (age-sex adjusted hazard ratio 2.17, 95% CI 1.84-2.57). After adjusting for deprivation and clinical risk factors the hazard ratio was still 1.71 (95% CI 1.44-2.02). For Asian people the age-sex adjusted hazard ratio was 1.95 (95% CI 1.73-2.18) which was reduced to 1.62 after full adjustment for other risk factors (95% CI 1.43-1.82).

Dyer (BMJ 2020, see ***below***) discussed the excess COVID-19 deaths among African-Americans, an observation related at least in part to a higher burden of underlying medical conditions such as diabetes, hypertension, obesity, and asthma among African-Americans. The author noted that the true scale of the disparity is unknown because few states and counties include racial data in their reporting. Another factor likely to be at play is the fact that many black people in the US work in essential jobs or in jobs that require in-person human interaction or cannot be done from home. Many also live in southern states, where Republican governors delayed lockdowns or played down the threat from the virus.

Khalatbari-Soltani (J Epidemiol Community Health. 2020, see ***below***) observed that from 29 studies that reported the characteristics of patients with COVID-19 and their potential risk factors, only one study reported the occupational position of patients with mild or severe disease. This brief overview highlighted that important **socioeconomic** characteristics are being overlooked when data are collected. A systematic recording of socioeconomic characteristics

of patients with COVID-19 would be beneficial to identify most vulnerable groups, to identify how socioeconomic position relates to COVID-19 and to develop equitable public health prevention measures, guidelines and interventions.

Zhao (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.03.11.20031096v2) compared the ABO **blood group** distribution in 2,173 patients with COVID-19 confirmed by SARS-CoV-2 test from three hospitals in China with that in normal people from the corresponding regions. The results showed that blood group A was associated with a higher risk for acquiring COVID-19 compared with non-A blood groups (OR 1.12, 95% CI 1.02-1.43), whereas blood group O was associated with a lower risk for the infection compared with non-O blood groups (OR 0.67, 95% CI 0.60-0.75). This early study should encourage further investigation of the relationship between the ABO blood group and COVID-19 susceptibility. Interestingly, as noted by Dai (Eur J Prev Cardiol 2020, see ***below***), the A allele of the ABO blood group has been associated with an increased risk of developing cardiovascular diseases.

Clinical prediction models

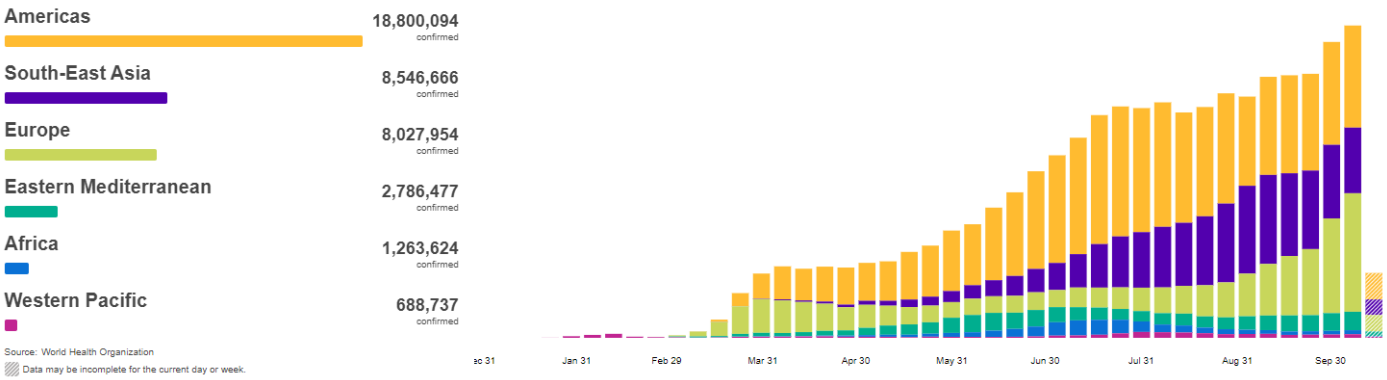
Clinical prediction models combine patient characteristics, biomarkers and other predictors to estimate individual risks related to COVID-19. As the vast majority of countries have limited testing and ICU capacity, case identification and prognosis tools could play a crucial role in containment and mitigation strategies, as well as efficient triage. Various international studies have already described attempts at generating clinical prediction models for COVID-19. As listed in the living reviewing by Wynants (BMJ 2020, see ***below***), 7 models are proposed for identifying people at risk in the general population; 33 diagnostic models for detecting COVID-19, 75 diagnostic models based on medical imaging (including deep learning on CT or Rx), 10 to diagnose disease severity), and 107 prognostic models for prediction mortality risk, intensive care unit admission, ventilation, intubation, or length of hospital stay. The most frequently reported predictors of diagnosis and prognosis of covid-19 are vital signs (incl. body temp, respiratory rate, oxygen saturation), age, comorbidities, and image (CT, Rx) features, in addition to flu-like symptoms for diagnosis and sex, C-reactive protein, and lymphocyte counts for prognosis. Reported index estimates (which provide an estimate of the ability of the model to discriminate) ranged from 0.71 to 0.99 in prediction models for the general population, from 0.65 to 0.99 in diagnostic models, from 0.80 to 0.99 for diagnostic severity models, for 0.70 to >0.99 for imaging models, and from 0.54 to 0.99 in prognostic models. All studies were rated at high or unclear risk of bias, mostly because of mainly because of model overfitting, inappropriate model evaluation (e.g. calibration ignored), and use of inappropriate data sources. Therefore, their performance estimates are probably optimistic and not representative for the target population. Reporting quality varied substantially between studies. Similarly, Hooli (Clin Inf Dis 2020, see ***below***) questioned the reproducibility of four COVID-19 case prediction models presented in another study.

Distribution

Case count dashboards

A disease situation dashboard is available on the WHO website, which presents the number of confirmed cases globally, per region and per country over time (https://covid19.who.int/). A snapshot of the number of cases reported (total and weekly) per region as of October 20 2020 12:00 CET is provided in ***Figure 16***.

Figure 16 Snapshot of the WHO COVID-19 dashboard as of October 20 2020 12:00 CET (confirmed disease cases reported weekly and total per region)

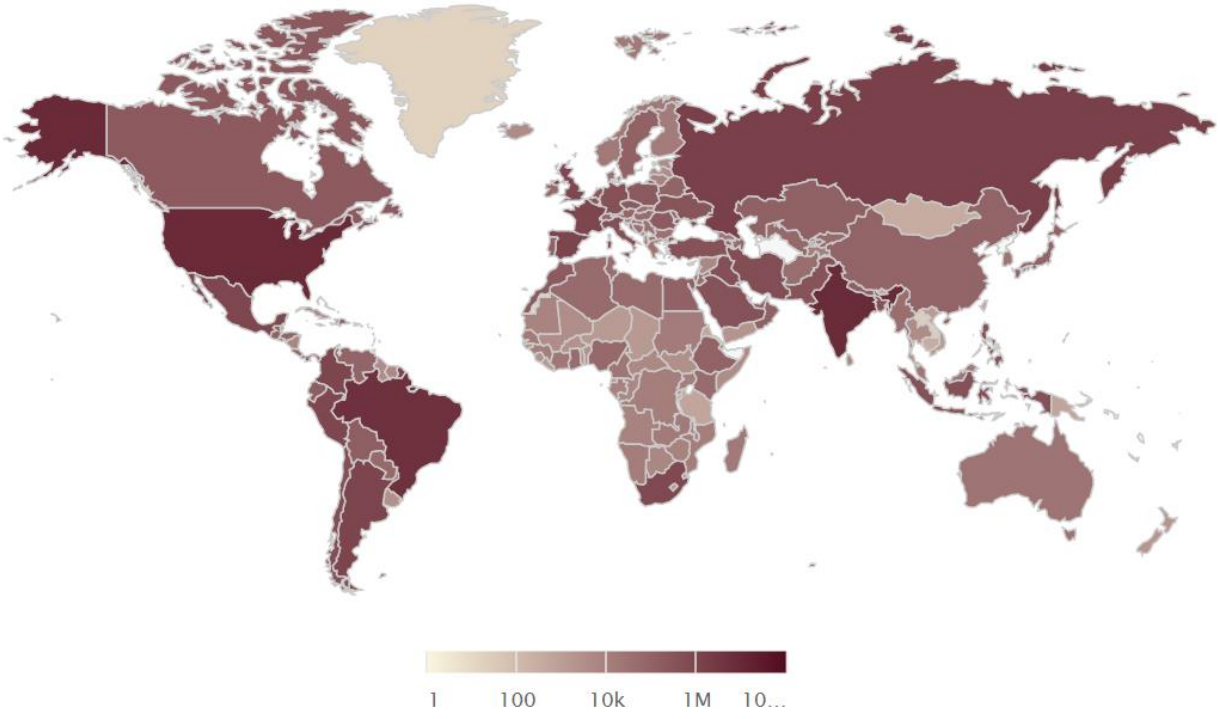


The Johns Hopkins University developed its own dashboard to visualize and track the reported cases of COVID-19 on a daily timescale (Dong Lancet Infect Dis 2020, see ***below***). The dataset can be found at https://coronavirus.jhu.edu/map.html. It is collected from various sources, including WHO, U.S. CDC, ECDC China CDC (CCDC), NHC and DXY. DXY is a Chinese website that aggregates NHC and local CCDC situation reports in near real-time, and has provided more current regional case estimates than the national level reporting organizations at the beginning of the epidemic.

HealthMap has made an interactive map for SARS-CoV-2 available at https://www.healthmap.org/covid-19/. It offers near-real-time geolocated updates from various sources to better understand the progression of the pandemic.

Another interesting resource is the worldwide timeline of cases provided by Worldometers (https://www.worldometers.info/coronavirus/worldwide-graphs/). This website provides an animated presentation of the evolution of the total number of cases per country from January 14 2020 (cases timeline). A snapshot of the world map as of October 20 2020 is provided by ***Figure 17***.

Figure 17 Snapshot of the worldometers world map as of October 20 2020



Data quality issues

Koh (Ann Acad Med Singapore 2020, see ***below***) highlighted the multiple issues affecting the accuracy of COVID-19 case counts. A serious issue highlighted by Lau (J Microbiol Immunol Infect 2020, see ***below***) relates to inconsistencies in reporting COVID-19 cases. The authors presented preliminary data indicating that countries with lower Health Access Quality-index may either underreport COVID-19 cases or are unable to adequately detect them. Another problem relates to variability in the case definitions used for reporting (see Case definition ***above***). A change in the case definition in China in February, for instance, led to a spike in the reported figures (https://www.sciencemediacentre.org/expert-reaction-to-the-latest-change-in-case-definitions-in-china-for-covid-19/).

Interestingly, Boëlle (EuroSurv 2020, see ***below***) indicated that several French regions where COVID-19 has been reported showed a renewed increase in ILI cases in the general practice-based Sentinelles network. The number of excess cases by region from 24 February to 8 March 2020 was computed and a correlation found with the number of reported COVID-19 cases, which suggested larger circulation of SARS-CoV-2 in the French population than apparent from confirmed cases.

Of note, WHO issued guidance to member states on the implementation of global surveillance of COVID-19 (lasted version dated August 7 2020, see https://www.who.int/publications/i/item/who-2019-nCoV-surveillanceguidance-2020.7). The objectives of this global surveillance are to monitor trends of the disease where human to human and/or zoonotic transmission occurs; rapidly detect new cases in countries where the virus is not circulating; provide epidemiological information to conduct risk assessment at the national, regional and global level; and provide epidemiological information to guide response measures.

Desjardins (Appl Geogr 2020, see ***below***) utilized a prospective space-time scan statistic to detect emerging clusters of COVID-19 in the United States at the county level. This prospective approach can be useful for state and local health departments to monitor the outbreaks in a timely fashion. The system adds updated COVID-19 counts and reruns the statistic to identify new emerging clusters; while also tracking the previously detected clusters to determine if they are growing or shrinking in magnitude. Doing so can help determine if current mitigation and isolation techniques are effective at curbing the spread of COVID-19.

Seroepidemiology

For later phases of pandemic control, when the key questions involve when, where, and how to lift confinement measures and relax social distancing constraints, serological testing to measure antibody responses to the virus becomes paramount to refine understanding of transmission intensity and population susceptibility (Bryant Sci Imm 2020, see ***below***). At the population level, representative cross-sectional serosurveys can provide aggregate "snapshots" of infection history and immunity of a population. Clapham (Em Inf Dis 2020, see ***below***) presented the various seroepidemiologic study designs that may help determine SARS-COV-2 transmission and immunity.

Up to now, despite the progression of the epidemic, published data point to a very limited level of immunity in the populations tested. In Geneva, Switzerland, for example, a study by Stringhini (Lancet 2020, see ***below***) enrolled 2766 participants from 1339 households between April 6 and May 9, 2020. In the first week, a seroprevalence of 4·8% (95% CI 2·4-8·0, n=341) was found. The estimate increased to 8·5% (5·9-11·4, n=469) in the second week, to 10·9% (7·9-14·4, n=577) in the third week, 6·6% (4·3-9·4, n=604) in the fourth week, and 10·8% (8·2-13·9, n=775) in the fifth week. Individuals aged 5-9 years (relative risk [RR] 0·32 [95% CI 0·11-0·63]) and those older than 65 years (RR 0·50 [0·28-0·78]) had a significantly lower risk of being seropositive than those aged 20-49 years.

In Spain, in a population sampled from April 27 to May 11 2020, Pollan found a seroprevalence of 5·0% (95% CI 4·7–5·4) by the point-of-care test and 4·6% (4·3–5·0) by immunoassay, with a specificity–sensitivity range of 3·7% (3·3–4·0;

both tests positive) to 6·2% (5·8–6·6; either test positive), with no differences by sex (Lancet 2020, see ***below***). Lower seroprevalence was observed in children younger than 10 years (<3.1% by the point-of-care test). There was substantial geographical variability, with higher prevalence around Madrid (>10%) and lower in coastal areas (<3%). Seroprevalence among 195 participants with positive PCR more than 14 days before the study visit ranged from 87·6% (81·1–92·1; both tests positive) to 91·8% (86·3–95·3; either test positive). In 7273 individuals with anosmia or at least three symptoms, seroprevalence ranged from 15·3% (13·8–16·8) to 19·3% (17·7–21·0). Around a third of seropositive participants were asymptomatic, ranging from 21·9% (19·1–24·9) to 35·8% (33·1–38·5).

Havers (JAMA Int Med 2020, see ***below***) reported the outcome of a study that analysed serum samples from 16 025 persons in the U.S. (55.2% of whom were women; 7.5% were 18 years or younger and 36.2% were 65 years or older). Most specimens from each site had no evidence of antibodies to SARS-CoV-2. Adjusted estimates of the proportion of persons seroreactive to the SARS-CoV-2 S protein ranged from 1.0% in the San Francisco Bay area (collected April 23-27) to 6.9% of persons in New York City (collected March 23-April 1). The estimated number of infections ranged from 6 to 24 times the number of reported cases; for 7 sites (Connecticut, Florida, Louisiana, Missouri, New York City metro area, Utah, and western Washington State), an estimated greater than 10 times more SARS-CoV-2 infections occurred than the number of reported cases.

Similar low seroprevalence data were reported by other studies conducted in the U.S. In a random sample of Indiana residents aged ≥12 years, the estimated prevalence of current or previous SARS-CoV-2 infection in late April 2020 reached 2.79% (Menachemi MMWR 2020, see ***below***). And in two counties in metropolitan Atlanta during April 28–May 3, a community seroprevalence survey, using a two-stage cluster sampling design and serologic testing, estimated that 2.5% of the population had antibodies to SARS-CoV-2 (Biggs MMWR 2020, see ***below***).

Some studies also specifically focused on health care personnel. For instance, in the U.S., Stubblefield (Clin Inf Dis 2020, see ***below***) found that among 249 healthcare personnel who worked in hospital units with COVID-19 patients for one month, 19 (7.6%) tested positive for SARS-CoV-2 antibodies. In China, Chen reported 17.14% (18/105) of health care workers being seropositive (J Inf 2020, see ***below***).

Virus migration pathways

Using phylodynamic analyses, Yang (Em Micr Inf Dis 2020, see ***below***) identified four genetic clusters, found to be responsible for the major outbreaks that subsequently occurred in various countries. Data showed that derivative strains of the original virus have been transmitted worldwide and contributed to the early outbreak of COVID-19. As illustrated in ***Figure 18***, SS1 strains were transmitted mainly in Asia and the US but were less prevalent in other parts of the world. SS2 and SS3 strains were transmitted mainly in Asian countries other than China, as well as Europe from mid-January to mid-February 2020. SS4 strains were transmitted mainly in Europe at the beginning of the pandemic and were then transmitted to all over the world. The data are consistent with those obtained earlier by Forster (PNAS 2020, see ***below***), who analysed 160 complete genomes of SARS-CoV-2 and identified three central variants, namely Type A, B and C. Type A was the ancestral virus. Type B strains carried the C8782T and T28144G mutations, which was equivalent to SS1. Type C, which carried the G26144T change, was equivalent to SS2. Forster found that Type A and C were mainly transmitted in Europe and America, whereas Type B was the most common type in East Asia.

Figure 18. Transmission of SARS-CoV-2 in different parts of the world (from Yang Em Micr Inf Dis 2020)

Factors impacting the distribution of the epidemic

In different countries, the COVID-19 epidemic takes variable shapes and forms in how it affects communities. Until now, the insights gained on COVID-19 have been largely dominated by the COVID-19 epidemics and the lockdowns in China, Europe and the USA. However, as noted in July 2020 by Van Damme (BMJ Glob Health 2020, see ***below***), the variety of global trajectories is little described, analysed or understood.

A study by Yao (Eur Resp J 2020, see ***below***), for instance, aimed to determine the association of meteorological factors with transmission of COVID-19. Associations of meteorological factors (including temperature, relative humidity and UV radiation) with the spread ability of COVID-19 in various Chinese cities (from early Jan to early March) were analysed. The study did not support the hypothesis that high temperature and UV radiation can reduce the transmission of COVID-19. However, a study by Liu (Sci Total Environ 2020, see ***below***) concluded that meteorological factors play an independent role in the COVID-19 transmission after controlling population migration. Local weather condition with low temperature, mild diurnal temperature range and low humidity likely favour the transmission.

Martelletti (SN Compr Clin Med 2020, see ***below***) showed how the Italian Northern Regions, which have been the most affected by COVID-19, are also those with a high amount of atmospheric particulate matter (PM10 and PM2.5) going above the standard limit of 50 µg/m3 per day in the month of February 2020. This relationship was also illustrated by comparing the nitrogen dioxide emissions and the COVID-19 case fatality in Northern Italy in January 2020. However, epidemiological studies in multiple geographic regions affected by the Covid-19 pandemic remain to be conducted to confirm the association with air pollution.

Arias-Reyes (Respir Physiol Neurobiol. 2020, see ***below***) suggested a lower incidence of COVID-19 in people living at high altitude (above 3000m from sea level).

Across the continents and specifically in Africa, all index cases were travel related and multiple introductions events recorded. In order to disentangle populational mediated intrinsic factors potentially limiting COVID-19 spread locally, it is also crucial to identify if there are distinguishing mutations in the SARS-CoV-2 genomes. Phylogenetic analysis and amino acid sequence alignments of the S and replicase (NSP12) proteins showed a similarity between the African SARS-CoV-2 genomes and genomes in countries including China, Brazil, France, the United Kingdom, Italy, France and the

USA. A majority of African S proteins have a D614G substitution as shown in the alignment of the amino acid which was also identified to be predominant in Asian and European SARS-CoV-2 sequences (Longjohn, manuscript on bioRxiv : https://doi.org/10.1101/2020.09.08.287201). However, *in silico* studies using structural bioinformatics to assess the effect of D614G mutation on SARS-CoV-2 virulence and epidemiology suggest that this mutation may be neutral to protein function (Isabel, Sci Rep 2020, see ***below***). A pan-African study (52 countries) attempted to estimate the impact and possible trajectory of COVID-19 under different intervention scenarios (Frost, manuscript on medRxiv : https://doi.org/10.1101/2020.09.04.20188102). While their model provided estimates suggesting that the burden of severe disease caused by SARS-CoV-2 is likely to be high for the African continent, especially in populations with high prevalence of TB, HIV, and malnutrition, these projections did not take into account the populational socio-demographical characteristics which may limit natural spread. For example a regional study used a simple deterministic SIR model to understand the spread and percolation of SARS-CoV-in 16 West African countries (Honfo, manuscript on medRxiv : https://doi.org/10.1101/2020.09.04.20188532). The study revealed an overall relatively low proportion of susceptible individuals (1.2% across West Africa) but also highlighted local discrepancies (e.g. Guinea-Bissau and Cape Verde) that cannot be explained by interventions (lockdown) and other non-therapeutic measures alone. Mbow (Science 2020, see ***below***) discussed the possible factors that may contribute to lower prevalence and mortality rates caused by COVID-19 in Africa. Differences between Africa and the most affected countries in reliable reporting and death registration, lockdown stringency, demography (age-pyramid), sociocultural aspects, environmental exposures (hygiene hypothesis, microbiota), genetics, and the immune system (trained immunity and virtual memory T cells) could help to explain the continent experience of COVID-19. As such, Africa should be part of the roadmap for COVID-19 research. Although there are no available data on the immune responses in African COVID-19 patients, studies show clear differences in the activation, proinflammatory, and memory profiles of the immune cells not only in Africans versus Europeans but also among Africans with high and low exposure to microorganisms and parasites (Mbow Immunology 2014, see ***below***).

A MMWR report identified geographic differences in numbers of COVID-19 cases and deaths, cumulative incidence, and changes in incidence across U.S. jurisdictions (CDC COVID-19 Response Team MMWR Morb Mortal Wkly Rep 2020 April, see ***below***). These were interpreted as likely reflecting a combination of jurisdiction-specific epidemiologic and population-level factors, including 1) the timing of COVID-19 introductions; 2) population density; 3) age distribution and prevalence of underlying medical conditions among COVID-19 patients; 4) the timing and extent of community mitigation measures; 5) diagnostic testing capacity; and 6) public health reporting practices. The authors concluded that monitoring jurisdiction-level numbers of COVID-19 cases, deaths, and changes in incidence is critical for understanding community risk and making decisions about community mitigation, including social distancing, and strategic health care resource allocation.

In terms of research activities, various modelling studies analyse available information and make attempts at forecasting future spread of the disease (see ***Modelling key characteristics of the epidemic*** below).

Virus in the environment

Kampf (J Hosp Infect 2020, see ***below***) reviewed the literature on the persistence of human and veterinary coronaviruses on inanimate surfaces as well as inactivation strategies with biocidal agents used for chemical disinfection, e.g. in healthcare facilities. This analysis revealed that human coronaviruses such as SARS and MERS CoVs or endemic human CoVs can persist on inanimate surfaces like metal, glass or plastic for up to 9 days, but can be efficiently inactivated by surface disinfection procedures with 62-71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite within 1 minute. Other biocidal agents such as 0.05-0.2% benzalkonium chloride or 0.02% chlorhexidine digluconate were found less effective.

Similarly, Yeo (Lancet Gastroenterol Hepatol 2020, see ***below***) indicated that observations made with SARS and MERS CoVs support a relatively good viability of these viruses on surfaces depending on temperature and humidity. SARS-

CoV RNA was found in the sewage water of two hospitals in Beijing treating patients with SARS. When SARS-CoV was seeded into sewage water obtained from the hospitals in a separate experiment, the virus was found to remain infectious for 14 days at 4°C, but for only 2 days at 20°C.

Environmental sampling

A report by Ong (JAMA 2020, see ***below***) described the detection of virus RNA in the environment of 3 COVID-19 cases in isolation in Singapore. Samples from the environment of one of the patients yielded positive results by RT-PCR, with 13 (87%) of 15 room sites (including air outlet fans) and 3 (60%) of 5 toilet sites (toilet bowl, sink, and door handle) positive. The patient had upper respiratory tract involvement with no pneumonia and had 2 positive stool samples for SARS-CoV-2 on RT-PCR. Of note, only one personal protective equipment (PPE) swab, from the surface of a shoe front, was positive. All other PPE swabs were negative. All air samples were negative. In a subsequent study, the same authors (Ong Infect Control Hosp Epidemiol 2020, see ***below***) conducted a one-day PPE sampling study on 30 HCWs (doctors, nurses, and cleaners) caring for 15 confirmed SARS-CoV-2 infected patients with varying characteristics (i.e. day of illness, presence/absence of symptoms, RT-PCR Ct value). None was requiring ventilatory support and no aerosol generating procedures were carried out prior to or during sampling. Median time spent in the patient's room was 6 minutes for activities ranging from casual contact (e.g. administering medications, cleaning) to closer contact (e.g. physical examination, collection of respiratory samples). All samples (swabs from the entire front of goggles, front surface of N95 respirator, and front surface of shoes) were negative.

Environmental surveillance was also performed by Cheng (Inf Contr Hosp Epidem 2020, see ***below***) in a patient with viral load of $3.3x10^6$ copies/ml (pooled nasopharyngeal/ throat swab) and $5.9x10^6$ copies/ml (saliva) respectively. SARS-CoV-2 was revealed in 1 (7.7%) of 13 environmental samples, but not in 8 air samples collected at a distance of 10 cm from patient's chin with or without wearing a surgical mask.

Another important study was conducted by Guo in a hospital in Wuhan (Em Inf Dis 2020, see ***below***) and showed that SARS-CoV-2 was widely distributed in the air and on object surfaces, implying a potentially high infection risk for medical staff and other close contacts. The environmental contamination was greater in the ICU than in the general COVID-19 ward. Moreover, SARS-CoV-2 aerosol distribution characteristics indicated that the transmission distance of SARS-CoV-2 might be 4 m. As of March 30, no staff members at this hospital had been infected with SARS-CoV-2, indicating that appropriate precautions could effectively prevent infection. In addition, these findings suggested that home isolation of persons with suspected COVID-19 might not be a good control strategy.

Liu (Nature 2020, see ***below***) measured viral RNA in aerosols in different areas of two Wuhan hospitals during the COVID-19 outbreak in February and March 2020. The concentration of SARS-CoV-2 RNA in aerosols detected in isolation wards and ventilated patient rooms was very low, but it was elevated in the patients' toilet areas. Airborne SARS-CoV-2 RNA in the majority of public areas was undetectable except in two areas prone to crowding. The authors suggested that SARS-CoV-2 may have the potential to be transmitted via aerosols.

During the initial isolation of 13 individuals with COVID-19 at the University of Nebraska Medical Center in the U.S.A., Santarpia (Sci Rep 2020, see ***below***) collected air and surface samples to examine viral shedding from isolated individuals. The authors detected viral contamination among all samples.

Failure to isolate viable (infectious) virus in **aerosols** has been commonly reported, and there has been controversy in the first months of the epidemic whether SARS-CoV-2 can be transmitted through aerosols. According to Lednicky (Int J Infect Dis 2020, see ***below***), this conundrum occurs because common air samplers can inactivate virions through their harsh collection processes. The authors then sought to resolve the question whether viable SARS-CoV-2 can occur in aerosols using VIVAS air samplers that operate on a gentle water-vapor condensation principle. Air samples were collected in the hospital room of two COVID-19 patients, one ready for discharge, the other newly admitted. Viable

SARS-CoV-2 was isolated from air samples collected 2 to 4.8 m away from the patients. The genome sequence of the SARS-CoV-2 strain isolated from the material collected by the air samplers was identical to that isolated from the newly admitted patient. Estimates of viable viral concentrations ranged from 6 to 74 TCID50 units/L of air. The data therefore indicated that patients with respiratory manifestations of COVID-19 produce aerosols in the absence of aerosol-generating procedures that contain viable SARS-CoV-2, and that these aerosols may serve as a source of transmission of the virus.

In a study by Wang (Int J Inf Dis 2020, see ***below***), **sewage** samples were positive from inlets of the sewage disinfection pool, but negative from the outlet of the last sewage disinfection pool. Moreover, no viable virus was detected by culture. The monitoring data in this study suggested that strict disinfection and hand hygiene measures could decrease the hospital-associated COVID-19 infection risk of the staffs in isolation wards.

La Rosa (Water Res 2020, see ***below***) reviewed available information on other coronaviruses in water environments. 12 publications were included. The data suggested that: i) CoV seems to have a low stability in the environment and is very sensitive to oxidants, like chlorine; ii) CoV appears to be inactivated significantly faster in water than non-enveloped human enteric viruses with known waterborne transmission; iii) temperature is an important factor influencing viral survival (the titer of infectious virus declines more rapidly at 23°C-25 °C than at 4 °C); iv) there is no current evidence that human coronaviruses are present in surface or ground waters or are transmitted through contaminated drinking-water. Ahmed (Sci Total Envir 2020, see ***below***) reported the first confirmed detection of SARS-CoV-2 in untreated wastewater in Australia. SARS-CoV-2 RNA was concentrated from wastewater in a catchment in Australia and viral RNA copies were enumerated using RT-qPCR, resulting in two positive detections within a six-day period from the same wastewater treatment plant.

Experimental conditions

van Doremalen (NEJM 2020, see ***below***) found that SARS-CoV-2 remained viable in aerosols (generated with the use of a three-jet Collison nebulizer and fed into a Goldberg drum to create an aerosolized environment) for at least 180 minutes, with a reduction in infectious titer 3 hours post-aerosolization from $10^{3.5}$ to $10^{2.7}$ CID50/L (mean across three replicates). This reduction in viable virus titer was relatively similar to the reduction observed in aerosols containing SARS-CoV-1. A subsequent report by Fear (Em Inf Dis 2020, see ***below***) agreed with these conclusions. In this study, the authors analysed the virus dynamic aerosol efficiency using 3 different nebulizers to generate viral aerosols. The aerosol size distributions produced by the generators used, in mass median aerodynamic diameter, were 1–3 µm and had a geometric heterodispersity of ≈1.2–1.4. The data suggested retained infectivity and virion integrity for up to 16 hours. Of note, a fraction of naturally generated aerosols falls within the size distribution used in the experimental studies (<5 µm), which leads us to conclude that SARS-CoV-2-infected persons may produce viral bioaerosols that remain infectious for long periods after production through human shedding and airborne transport.

The virus was found most stable on plastic and stainless steel (van Doremalen NEJM 2020, see ***below***). Viable virus could be detected up to 72 hours post application, though by then the virus titer was greatly reduced (polypropylene from $10^{3.7}$ to $10^{0.6}$ TCID50/mL after 72 hours, stainless steel from $10^{3.7}$ to $10^{0.6}$ TCID50/mL after 48 hours).

Since the beginning of the pandemics, few authors have attempted to test a wider array of environmental and climatological conditions (temperature, humidity, surface texture) conducive to SARS-CoV-2 survival. This was even more required as summer-winter transition and colder temperatures coincided with school and factories re-opening and an easing of restrictive isolation measures in the Northern hemisphere. Kwon (manuscript on bioRxiv : https://doi.org/10.1101/2020.08.30.274241) tested SARS-CoV-2 stability on 12 material surfaces including nitrile glove, Tyvek, N95 mask, cloth, Styrofoam, cardboard, concrete, rubber, glass, polypropylene, stainless steel and galvanized steel under 3 conditions based on Midwestern U.S. weather. SARS-CoV-2 remained viable and infectious on surfaces for 1 to 4 days at indoor conditions (21°C/60% relative humidity, RH), 1 to 3 days during summer conditions

(25°C/70% RH) and over 7 days during spring/fall conditions (13°C/66% RH). They provide experimental evidence that the virus is significantly more stable on all surfaces under the outdoor spring/fall condition and suggests that virus stability on surfaces is highly dependent on temperature and RH. They conclude that prolonged virus survival on surfaces in spring/fall and winter might support SARS-CoV-2 transmission through contaminated fomites and potentially contribute to new outbreaks and/or seasonal occurrence in the post-pandemic era, a scenario described for influenza virus and other human coronaviruses (Kissler Science 2020, see ***below***).

Patient management

In China, a rapid advice guideline suitable for the first frontline doctors and nurses, managers of hospitals and healthcare sections, as well as community residents or public health persons has been provided by Jin in February 2020 (Mil Med Res 2020, see ***below***). This guideline covered disease screening and population prevention, diagnosis, treatment and control (including traditional Chinese Medicine), nosocomial infection prevention and control, and disease nursing of the 2019-nCoV.

WHO issued a document intended for clinicians taking care of patients with COVID-19, including those with mild, moderate, severe, and critical disease (interim guidance last updated on May 27, see https://www.who.int/publications/i/item/clinical-management-of-covid-19). Developed by a multidisciplinary panel of health care providers with experience in the clinical management of patients with COVID-19 and other viral infections, including SARS and MERS, as well as sepsis and acute respiratory distress syndrome (ARDS), this guidance should serve as a foundation for optimized clinical care to ensure the best possible chance for survival. The guidance stresses the importance of using investigational therapeutic interventions as part of randomized controlled trials.

In addition to this document, a huge number of publications describe both the disease course and clinical management of patients in China as well as in other countries. A few examples are provided in the following sections for illustrative purposes.

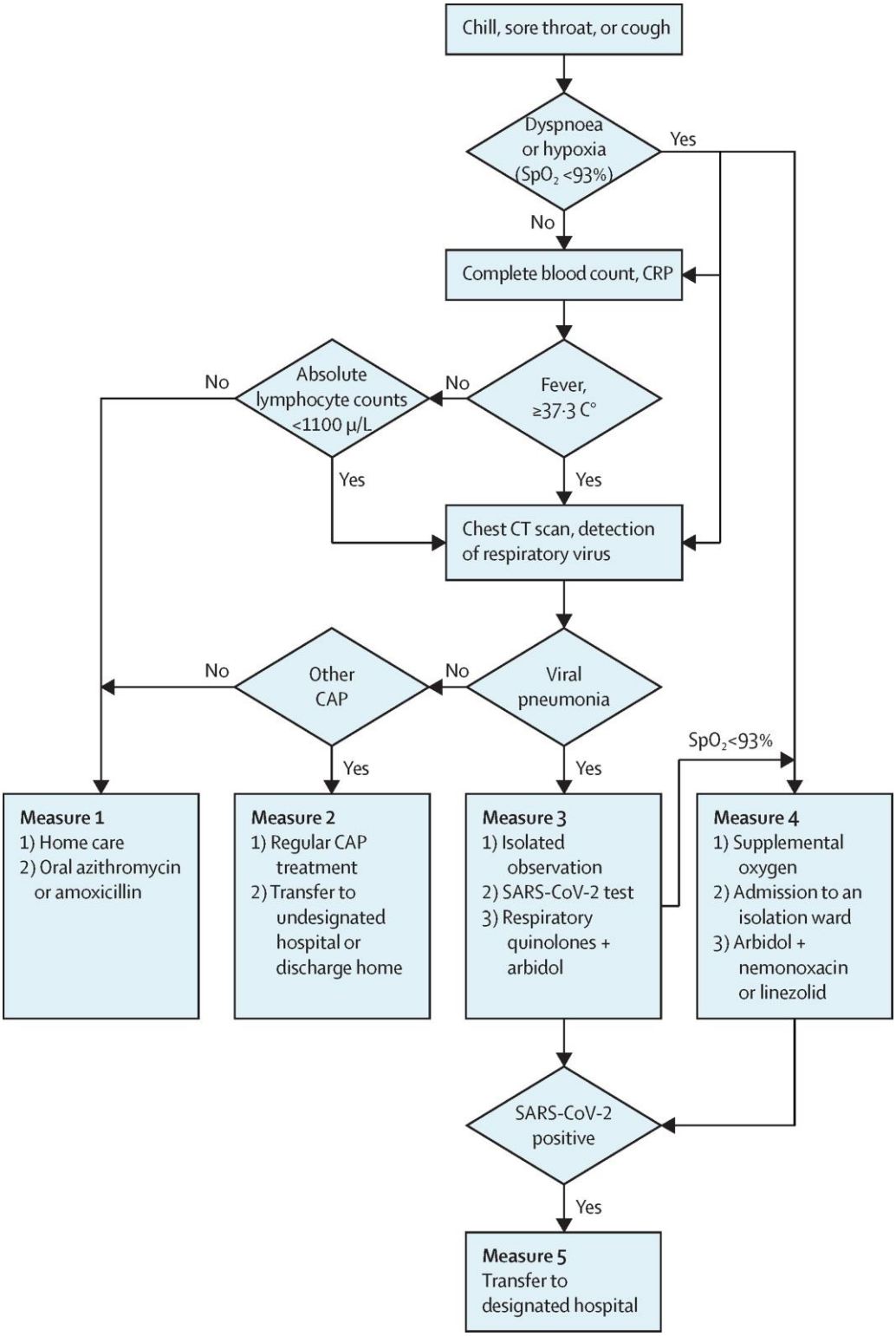
Triage and patient flow

A publication by Zhang (Lancet Resp Med 2020, see ***below***) indicates that one effective strategy for disease control in Wuhan was the establishment of fever clinics for triaging patients. The clinical strategies that were used in these adult fever clinics for COVID-19 management is illustrated by the flowchart presented in ***Figure 19***.

Many aspects of this algorithm would not be feasible in developing countries setting, as chest CT, differential blood counts, and CRP testing are not available. Ayebare (Lancet Resp Med 2020, see ***below***) proposed a modified COVID-19 screening algorithm for use in resource-limited settings that do not have established local transmission.

Hu (Acad Emerg Med 2020, see ***below***) provided a first exploration on 2 rapid scoring systems for critical ill patients with COVID-19, the Modified Early Warning Score (MEWS) and Rapid Emergency Medicine Score (REMS). The authors concluded that the REMS could provide emergency clinicians with an effective adjunct risk stratification tool for critical ill patients with COVID-19, especially for the patients aged<65 years. The effectiveness of REMS for screening these patients is attributed to its high negative predictive value.

Figure 19 Flow chart for treatment of COVID-19 in fever clinics in Wuhan China (CRP=C-reactive protein. CAP=Community-acquired pneumonia. SARS-CoV-2=severe acute respiratory syndrome corona virus 2)



Treatment practices

Numerous reports provided by various authors at the start of the epidemic in China described patient management for severe cases of COVID-19.

For instance, Wang, Chen et al. (Biosci Tr 2020, see ***below***) reported on the diagnosis and treatment of four patients with mild or severe COVID-19 pneumonia. All patients received antiviral treatment, including lopinavir/ritonavir

(Kaletra®, lopinavir 400 mg/ritonavir 100 mg, q12h, po), arbidol (0.2 g, tid, po), and Shufeng Jiedu Capsule (2.08 g, tid, po). The duration of antiviral treatment was 6-15 days. In addition, all patients were all given antibiotic treatment and started on supplemental oxygen, delivered by nasal cannula after admission to hospital.

Liu (Crit Care 2020, see ***below***) reported that patient management in Shenzhen was largely supportive, including intubation, early prone positioning, neuromuscular blockade, and extracorporeal membrane oxygenation (ECMO) according to the recommendations updated by China's National Health Committee. Low-dose systematic corticosteroids, lopinavir/ritonavir, and atomization inhalation of interferon were encouraged.

Murthy (JAMA 2020, see ***below***) noted that evidence-based treatment guidelines for ARDS should be followed, including conservative fluid strategies for patients without shock following initial resuscitation, empirical early antibiotics for suspected bacterial co-infection until a specific diagnosis is made, lung-protective ventilation, prone positioning, and consideration of extracorporeal membrane oxygenation for refractory hypoxemia.

Wang (Lancet 2020, see ***below***) reported on the classification of COVID-19 patients in 3 types for effective triage in a hospital in Wuhan. Patients with pneumonia were classified as type A. Basic treatments were provided, such as antivirals, antibiotics, oxygen therapy, and glucocorticoids. Type B patients had disease accompanied by serious comorbidities. Their pneumonia was managed and specific treatment plans were developed, including antihypertensives, hypoglycaemic therapy, and continuous renal replacement therapy. Critically ill patients were classified as type C. Attention was paid to organ function in these patients and necessary protective measures, including mechanical ventilation, glucocorticoids, antivirals, symptomatic treatments, and anti-shock therapy.

Based on the experience with 631 confirmed cases of COVID-19 (with a portion of critically ill patients whose ages ranged from 9 months to 96 years old), Sun (Ann Intensive Care 2020, see ***below***) reported a cure rate of confirmed cases of 96.67%in Jiangsu Province, far exceeding that of national Chinese data. The authors noted that essential strategies to improve outcomes consist of early detection of high-risk and critically ill patients. In Jiangsu Province, critical care was shifted forward. All COVID-19 patients were screened twice every day and respiratory rate (RR), heart rate (HR), SpO2 (room air) were monitored regularly. Once SpO2 < 93%, RR > 30/min, HR > 120/min or any signs of organ failure were observed, patients would be transferred to ICU. Intervention to prevent the progression of disease were then three-fold: (1) For patients with ARDS or pulmonary extensive effusion in CT scan, high-flow nasal cannula oxygen therapy or non-invasive mechanical ventilation was used to maintain positive end expiratory pressure to prevent alveolar collapse even if some of these patients did not have refractory hypoxemia. (2) Restrictive fluid resuscitation under the premise of adequate tissue perfusion was performed to relieve pulmonary oedema. (3) Awake prone position was attempted in patients which showed significant effects in improving oxygenation and pulmonary heterogeneity.

Duca (Emerg Med Pract. 2020, see ***below***) presented the Brescia-COVID Respiratory Severity Scale (BCRSS)/Algorithm, a step-wise approach to managing patients with confirmed/presumed COVID-19 pneumonia. The tool was described as in use in Italy for assessment, trending, and treatment recommendations.

A review paper by Nicola (Int J Surg 2020, see ***below***) also provided an interesting update on COVID-19 patient management. In addition, more than twenty nursing experts in China developed a consensus on holistic nursing care of patients with severe COVID-19, which included nursing assessment, nursing priorities, nursing goals, and 13 key points of nursing such as nursing of oxygen therapy and respiratory nursing (Int J Nurs Sci 2020, see ***below***).

Respiratory support

To reduce respiratory symptoms and improve prognosis, respiratory support is the most important means of life support, and non-invasive respiratory support systems, including various conventional oxygen therapies, non-invasive positive pressure ventilation (NPPV), and high-flow nasal cannula (HFNC), are most commonly used (Xia Chin Med J

2020, see ***below***). However, their efficacy and safety remain unclear, and whether they increase the risk of aerosol dispersion and disease transmission is particularly controversial (see Safety of procedures ***below***, and Ñamendys-Silva Lancet Respir Med 2020, see ***below***). The retrospective epidemiological study of 99 COVID-19 pneumonia patients in China revealed that NPPV is the most commonly used mechanical ventilation method for acute respiratory failure, with reported rates of using non-invasive and invasive mechanical ventilation of 13% and 4%, respectively. For strictly selected early-stage patients with mild-to-moderate (partial pressure of arterial oxygen [PaO2]/fraction of inspired oxygen [FiO2] > 200 mmHg) hypoxic respiratory failure and especially for units with limited numbers of invasive ventilators, it has been recommended that NPPV be attempted for short periods of time (1-2 hours) and to intubate immediately if no improvement is observed.

Of note, MacLaren (JAMA 2020, see ***below***) commented on the WHO interim guidelines making general recommendations for treatment of ARDS in the context of the COVID-19 epidemic, including that consideration be given to referring patients with refractory hypoxemia to expert centres capable of providing ECMO. ECMO being a resource-intensive, highly specialized, and expensive form of life support with the potential for significant complications, he recommended limiting support with ECMO to the most critically ill patients in regions with the extensive resources required to provide this therapy. In less well-resourced countries, his hypothesis is that many more lives will be saved by ensuring oxygen and pulse oximetry are widely available. Li (Chin Med J 2020, see ***below***) reported experience compared with that in patients receiving only conventional respiratory care, the fatality of those who had received ECMO was significantly lower (100% vs. 65%). However, a review by Henry (J Crit Care 2020, see ***below***) raised questions about real utility of ECMO in COVID-19 patients and concluded that further research is urgently needed. A more recent systematic review by Haiduc (J Card Surg 2020, see ***below***) also concluded that the recuperative effects of ECMO remain inconclusive.

Treatment of coagulopathy

The use of heparin in COVID-19 has been recommended by some expert consensus due to the risk of disseminated intravascular coagulation and venous thromboembolism. However, the efficacy of such treatment remains to be validated. A study in 449 patients with severe COVID-19, 99 of them receiving heparin for 7 days or longer suggested that anticoagulant therapy mainly with low-molecular weight heparin appears to be associated with better prognosis in severe COVID-19 patients meeting sepsis-induced coagulopathy criteria or with markedly elevated D-dimer (Tang J Thromb Haemost 2020, see ***below***). The 28-day mortality of heparin users was lower than that in non-users when considering patients with sepsis-induced coagulopathy score ≥4 (40.0% vs 64.2%, P=0.029), or D-dimer > 6-fold the upper limit of normal range (32.8% vs 52.4%, P=0.017).

Treatment options in pregnancy

Recent studies have identified remdesivir and chloroquine as candidate drugs for the treatment of COVID-19 (see ***Antiviral drugs*** below). Remdesivir appears to be safe in human pregnancies (Mulangu NEJM 2019, see ***below***) Although chloroquine and its metabolites cross the placenta, it may be safely used in all trimesters of pregnancy with no increased risk of adverse perinatal outcomes. Of note, chloroquine is a drug with a large volume of distribution and pharmacokinetic studies have shown significantly lower plasma drug concentrations in pregnancy (Karunajeewa Antimicr Ag Chemother 2010, see ***below***). Nevertheless, hydroxychloroquine has been reported as a common treatment options used in pregnant women (Diriba Eur J Med Res 2020, see ***below***). Lopinavir-ritonavir has also been evaluated in management of COVID-19. It was not studied in context of pregnancy complicated with respiratory infection, however in HIV-positive pregnancies, no increased risk of foetal anomalies, preterm birth or low birth weight infants was observed (Tookey BMC Infect Dis 2016, see ***below***). Conversely, ribavirin and baricitinib are teratogenic (Winthrop Nat Rev Rheumatol 2017, see ***below***; Kochhar Toxicol Appl Pharmacol 1980, see ***below***). Use of ribavirin has led to miscarriages, craniofacial and limb defects in animal studies and should be avoided, especially in early pregnancy.

In general, use of corticosteroids is not recommended as it may delay the virus clearance from the body. A common practice in obstetrics is to give corticosteroids for foetal lung maturity to those at risk of delivering prematurely. Travers (BMJ 2017, see ***below***) demonstrated that the lowest gestations receive the largest benefit from corticosteroids. Indeed, the number of mothers needed to treat with corticosteroids to prevent one neonatal death is six at 23 to 24 weeks but can increase to 798 women at 34 weeks. During this pandemic, balancing out the possible risks and benefits of corticosteroid use appeared important. McIntosh (Am J Perinatal 2020, see ***below***) examined the maternal risks and foetal benefits and recommended that no women COVID-19 positive or person under investigation (PUI) receive corticosteroids beyond 32 weeks. Use of drugs in pregnant women needs to be on the basis of solid evidence. Clinical trials are needed to prove the effectiveness of drugs and the effects on the foetus. WHO advised caution and careful risk-benefit analysis before using investigational therapeutic agents in pregnant women outside clinical trials and WHO did not recommend the use of corticosteroids for COVID-19.

Ethical issues

An ethically sound framework has been outlined in the Hastings Center's 3-tiered approach to a pandemic; namely, the duty to plan, the duty to safeguard, and the duty to guide. Furthermore, in the U.S.A. the landmarks proposed by the American College of Surgeons of transparency, advocacy, and commitment to support all those affected directly or indirectly clarify a way forward. Multiple ethical challenges have been raised by the COVID-19 pandemic. A few reports have made proposals to address them. For instance, Kramer (J Am Coll Surg 2020, see ***below***) provided a few recommendations based on the concepts highlighted above to questions such as "Do providers have the right to refuse to treat a COVID-19 positive patient, or do they have a professional duty to treat the patient, no matter how high the personal risk?" . The question of " How do we allocate scarce resources such as ICU beds, ventilators, and certain medications?" has also been addressed by Manelli (J Med Ethics 2020, see ***below***), who insisted on the relevance of a medical ethics perspective that does not place the burden of care and choice solely on physicians.

Diagnostics

Interim guidance to laboratories and stakeholders involved in laboratory testing of patients who meet the definition of suspected case of pneumonia associated with SARS-CoV-2 has been provided by WHO on March 19 2020 (https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117). Until validated diagnostic tests become available, the goals of diagnostic testing was to detect conventional causes of pneumonia early, to support disease control activities, and to work with reference laboratories that can perform pan-coronavirus detection and directed sequencing.

WHO took a three-pronged approach to enhance diagnostic capacity for COVID-19:

- Forming a network of specialized referral laboratories with demonstrated expertise in the molecular detection of coronaviruses. These international labs could support national labs to confirm COVID-19 cases and troubleshoot their molecular assays;
- Strengthening national capacity for detection of COVID-19 so that diagnostic testing can be performed rapidly without the need for overseas shipping. One way this has been achieved was through working with existing global networks for detection of respiratory pathogens such as, notably, the National Influenza Centers that support the Global Influenza Surveillance and Response System;
- Ensuring test availability. This has involved a) screening of SARS-CoV-2 PCR protocols from academic laboratories for validation data (e.g. limits of detection, specificity), b) looking for sequence alignment of established commercial coronavirus assays (e.g. SARS) to see if any were likely to be able to detect 2019-nCoV with high sensitivity, and c) working with commercial and non-commercial agencies with capacity to manufacture and distribute newly-developed SARS-CoV-2 PCR assays.

Specimen type

Lower respiratory specimens were soon considered likely to have a higher diagnostic value than upper respiratory tract specimens for detecting SARS-CoV-2 infection. However, Yang (on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.11.20021493v1) noted that no data on the difference of viral shedding between the upper and lower respiratory tract specimens was available. He reported that while viral RNAs could be detected in all the lower respiratory tract of severe cases, the situation was different for mild cases. Sputum specimen were recommended as most accurate for laboratory diagnosis of COVID-19, followed by nasal swabs.

A study by Zou (NEJM 2020, see ***below***) analysed the viral load in nasal and throat swabs obtained from 17 symptomatic patients in relation to day of onset of any symptoms. Higher viral loads were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat. This analysis suggests that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza and appears different from that seen in patients infected with SARS-CoV. While describing 2 cases, Han (Lancet Inf Dis 2020, see ***below***) suggested that sputum induction might be more helpful than throat swabs for the detection of SARS-CoV-2 RNA in convalescent patients. Recently, Mohammadi (EBioMed 2020, see ***below***) performed a systematic review and meta-analysis of studies comparing respiratory sampling strategies for the detection of SARS-CoV-2 RNA. The inclusion criteria were studies that assessed at least two respiratory sampling sites (oropharyngeal swab, nasopharyngeal swab, and sputum) in participants with COVID-19. The authors identified 11 studies that met the inclusion criteria, with SARS-CoV-2 testing results from a total of 3442 respiratory tract specimens. Compared to nasopharyngeal swab sampling, sputum testing resulted in significantly higher rates of SARS-CoV-2 RNA detection while oropharyngeal swab testing had lower rates of viral RNA detection. Earlier sampling after symptom onset was associated with improved detection rates, but the differences in SARS-CoV-2 RNA detection by sampling method was consistent regardless of the duration of symptoms.

Zhang (J Med Virol 2020, see ***below***) presented PCR testing results on stool and oropharyngeal swabs specimens from 14 patients.

A larger study analysed a total of 1070 specimens of different types that were collected from 205 patients with COVID-19 (Wang JAMA 2020, see ***below***). Bronchoalveolar lavage fluid specimens showed the highest positive rates (14 of 15; 93%), followed by sputum (72 of 104; 72%), nasal swabs (5 of 8; 63%), fibrobronchoscope brush biopsy (6 of 13; 46%), pharyngeal swabs (126 of 398; 32%), faeces (44 of 153; 29%), and blood (3 of 307; 1%). None of the 72 urine specimens tested positive.

Alternative samples

A manuscript by Srivatsan (on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.04.22.056283v1) suggested the possibility to use a dry swab without transport medium for RT-PCR testing.

Khoubnasabjafari (Bioanalysis 2020, see ***below***) suggested exhaled breath condensate (EBC) as a sample for RT-PCR. EBC is a condensed form of small droplets of lung lining fluid which is normally exhaled and contains a variety of components from small ions to proteins and organelles, even viruses, fungi and bacteria. Technical tips for improving the quality and quantity of extracting nucleic acid from EBC samples have been reported. The same procedure with some modifications could be used to detect the genome of SARS-CoV-2 by RT-PCR. EBC samples could be easily collected using a simple cold trap, commercially available EBC sampling device (such as EcoScreen® or RTube®) or even using a tube passing water-ice mixture. The mechanism of sample collection by these devices is cooling down the temperature of the collection chamber from 0 to -25°C. Collection of EBC is simple, well tolerated by sample donors and no adverse effects have been reported so far, therefore it could be employed for sampling on a large scale to screen COVID-19 suspected patients.

The potential breath-borne volatile organic compound (VOC) biomarkers for COVID-19 are other potential candidates to develop rapid diagnostic test. In particular, the monitoring of ethyl butanoate, butyraldehyde and isopropanol could lend considerable support in rapidly screening COVID-19; and alerting the presence of COVID-19 patient in particular environments (Chen, manuscript on medRxiv : https://doi.org/10.1101/2020.06.21.20136523). Breath test are currently being developed by US-based Canary Health Technologies and clinical trials under discussion in the UK, the USA and South Africa (Promed Archive Number: 20200621.7492311 : https://promedmail.org/promed-post/?id=7492311). The exhaled breath is sampled directly utilizing Airostotle's breath sensor system and a response is given in under 5 minutes. Airostotle has an array of differentially selective sensors that show interactions with VOCs in the exhaled breath of users. This sensor data creates a breath signature, a digital pattern of sensor response changes for the individual sensors that reflects the unique profile of the breath VOC mixture, that can be furthered classified using Artificial Intelligence. These breath patterns can be stored in an online database (a "breath-cloud") and coupled to clinical data. Comparison of the digitized breath patterns of a suspected subject to the breath-cloud allows for a rapid decision on the presence or absence of a pathogen (https://www.canaryhealthtech.com/news/preparing-for-pandemics-using-canary-health-technologies-cloud-based-rapid-breath-analysis-platform).

Self-collection

Molecular testing (PCR) using specimens collected from nasopharyngeal and/or oropharyngeal swabs is the standard screening approach for COVID-19. The method requires costly laboratory equipment and healthcare professionals that limit its use for large-scale screening of mild or asymptomatic patients. Self-collection kits for use in the home could remedy this and have consequently received great attention. In April, 2020, a self-collection kit from LapCorp was the first such kit to be approved by the FDA (Liao Adv Biosyst 2020, see ***below***). In the following month, May 2020, another kit developed by Everlywell received FDA approval, and more kits are evidently on their way to the market. Various authors reported data supporting the feasibility of this approach. Wehrhahn (J Clin Virol 2020, see ***below***), for instance, successfully evaluated the self-collection of nasal and throat swabs in a cohort of 236 patients.

Testing methods

Udugama (ASC nano 2020, see ***below***) presented an overview on the techniques used at the start of the epidemic, as well as on emerging diagnostic methods in March 2020. More recently, a review by Ravi (Biosens Bioelectron 2020, see ***below***) focused on molecular and serological assays with FDA Emergency Use Authorization. A list of assays commercially available for diagnosis of COVID-19 is updated by FIND (https://www.finddx.org/covid-19/pipeline/). Assays that are still in development stage are also presented. As indicated by Premraj (Diagnostics Basel 2020, see ***below***), there are now serious debates globally and regionally on the sensitivity and specificity of these tests and about the overall accuracy and reliability of the tests for decision making on COVID-19 control strategies.

Molecular methods

In April 2020, a review by Shen (J Pharm Anal 2020, see ***below***) summarized available detection methods for SARS-CoV-2 nucleic acid. The paper is short, but provides very clear explanations about the different methods that have been developed. A list of currently available molecular assays can be found at FIND (https://www.finddx.org/covid-19/pipeline/?section=molecular-assays#diag_tab).

RT-PCR

Initially developed RT-PCR assays

In acute respiratory infection, RT-PCR is routinely used to detect causative viruses from respiratory secretions. Early reports presented various assays for COVID-19 diagnosis. A real-time reverse-transcription PCR (rtRT-PCR) was used to identify SARS-CoV-2 through preliminary and validation detection of its E gene, RNA-dependent RNA polymerase (RdRp) gene, and N gene (Yu Micr Inf 2020, see ***below***). Chu (Clin Chem 2020, see ***below***) reported the development of two 1-step quantitative rtRT-PCR assays detecting the ORF1b and N regions of the viral genome. The primer and

probe sets were designed to react with SARS-CoV-2 and its closely related viruses, such as SARS coronavirus. These assays were evaluated using a panel of positive and negative controls and shown to have a dynamic range of at least seven orders of magnitude ($2x10^{-4}$-2000 TCID50/reaction).

Fluorescence-based quantitative PCR kit were rapidly distributed by the Chinese CDC for laboratory confirmation of disease in China. And a whole array of commercial tests became available. Wang (on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.12.20022327v2) reported for instance the use of a detection kit (Bioperfectus, Taizhou, China) to detect the ORF1ab gene and the N gene using real-time RT-PCR. Positive results on both the ORF1ab gene and the N gene are required for laboratory confirmation of the disease.

In Europe, the envelope (E)-gene screening test as published by Corman (Euro Surv 2020, see ***below***) has been widely implemented.

Sharfstein (JAMA 2020, see ***below***) and Babiker (Am J Clin Pathol 2020, see ***below***) provided a detailed explanation of the issues faced in the USA at the beginning of the epidemic, which delayed COVID-19 PCR testing in the country. Lu (Em Inf Dis 2020, see ***below***) described the design and validation of the US CDC rRT-PCR panel and presented comprehensive data on its performance with multiple specimen types and clinical specimens. The panel consisted of 3 RT-PCR assays targeting the N gene. The US FDA issued an Emergency Use Authorization on Feb 4 2020 to enable emergency use of this panel.

Improving PCR assays

Chan (J Clin Microb 2020, see ***below***) developed a novel real-time RT-PCR assay targeting the RNA-dependent RNA polymerase (RdRp)/helicase (Hel) (COVID-19-RdRp/Hel assay). The assay has a low limit of detection (1.8 TCID50/ml with genomic RNA and 11.2 RNA copies/reaction with in vitro RNA transcripts). It was compared to the RdRp-P2 assay currently used in European laboratories. Among 273 specimens from 15 patients with laboratory-confirmed COVID-19 in Hong Kong, 77 (28.2%) were positive by both the COVID-19-RdRp/Hel and RdRp-P2 assays. The COVID-19-RdRp/Hel assay was positive for an additional 42 RdRd-P2-negative specimens [119/273 (43.6%) vs 77/273 (28.2%), P<0.001], including 29/120 (24.2%) respiratory tract specimens and 13/153 (8.5%) non-respiratory tract specimens. The mean viral load of these specimens was 3.21×10^4 RNA copies/ml (range, 2.21×10^2 to 4.71×10^5 RNA copies/ml). The COVID-19-RdRp/Hel assay did not cross-react with other human-pathogenic coronaviruses and respiratory pathogens in cell culture and clinical specimens, whereas the RdRp-P2 assay cross-reacted with SARS-CoV in cell culture.

Won (ExpNeurobiol 2020, see ***below***) presented a low cost, rapid alternative RT PCR protocol for COVID-19 diagnosis, composed of specimen self-collection by the patient via pharyngeal swab, Trizol-based RNA purification, and SYBR Green-based RT PCR.

Automated platforms

Pfefferle (Euro Surveill 2020, see ***below***) evaluated the performance of a molecular assay for detection of SARS-CoV-2 on a high-throughput platform, the cobas 6800, using the 'open channel' for integration of a laboratory-developed assay. The authors observed good analytical performance in clinical specimens. The fully automated workflow enabled high-throughput testing with minimal hands-on time, while offering fast and reliable results.

Cepheid announced that it has received Emergency Use Authorization (EUA) from the U.S. FDA for Xpert® Xpress SARS-CoV-2, a rapid molecular diagnostic test for qualitative detection of SARS-CoV-2 (http://cepheid.mediaroom.com/2020-03-21-Cepheid-Receives-Emergency-Use-Authorization-from-FDA-for-Rapid-SARS-CoV-2-Test). The test has been designed to operate on any of Cepheid's automated GeneXpert® Systems, with a detection time of approximately 45 minutes.

Validation data & assay limitations

Xie (Int J Inf Dis 2020, see ***below***) compared nucleic acid amplification testing performed with 3 different fluorescent RT-PCR kits on different samples, including oropharyngeal swab, blood, urine and stool. Nine out of the 19 patients tested were found positive for SARS-CoV-2 using oropharyngeal swab samples, and the virus nucleic acid was also detected in eight of these nine patients using stool samples. None of positive results was identified in the blood and urine samples. Similar data were obtained with the 3 kits.

Of note, a lack of assay sensitivity was reported by Xie (Radiol 2020, see ***below***), who described five patients with SARS-CoV-2 infection who had initial negative RT-PCR results in mouth swabs but typical imaging findings, including ground-glass opacity (5 patients) and/or mixed ground-glass opacity and mixed consolidation (2 patients). All patients were eventually confirmed with SARS-CoV-2 infection by repeated swab tests. Similar cases were reported by various authors:

- Huang (Radiol 2020, see ***below***).
- Winichakoon (J Clin Microb 2020, see ***below***) reported a case of COVID-19 pneumonia diagnosed from bronchoalveolar lavage fluid in Thailand, who initially had negative tests from nasopharyngeal/oropharyngeal swabs.
- A publication by Wang, Kang et al. (J Med Vir 2020, see ***below***) further illustrates the sensitivity limitation of current RT-PCR based diagnosis, previously reported by others. Although the paper does not provide details, the authors described a COVID-19 case not confirmed by SARS-CoV-2 RT-qPCR testing at the first three evaluations within three weeks, before bronchoalveolar lavage fluid was acquired and results from both RT-qPCR and next-generation sequencing (NGS) testing became positive for SARS-CoV-2.
- Ruan (Chin Med J 2020, see ***below***) presented a case with negative RT PCR result until day 11 of disease onset.

Interestingly, a study by Li, Yao et al. (J Med Vir 2020, see ***below***) evaluated the sensitivity of RT-PCR testing on sequential samples. The study illustrated well on one hand the importance of retest for improving detection of positive cases, and on the other hand the instability of results over time in a same patient.

Wang (Clin Chem 2020, see ***below***) showed that the limit of detection (LOD) of the six commercial kits approved in China differ substantially, with the poorest LODs likely leading to false-negative results when RT–PCR is used to detect SARS-CoV-2 infection.

Rhoads (J Clin Microbiol 2020, see ***below***) compared the Abbott ID Now, Diasorin Simplexa, and CDC FDA EUA methods for the detection of SARS-CoV-2 from nasopharyngeal and nasal swabs. The 95% CIs for the positive percent agreement was overlapping for the ID Now and Simplexa assays when using the modified CDC method as the reference standard. The sample size of this study was not large enough to conclude one of these assays had clearly superior or inferior performance for the detection of SARS-CoV-2 from upper respiratory specimens in liquid transport media.

Another report by Moran (J Clin Microbiol 2020, see ***below***) compared results from specimens tested with Cepheid Xpert Xpress SARS-CoV-2 and Roche cobas SARS-CoV-2 assays. Of these 103 specimens, 42 tested positive and 60 tested negative with both systems for agreement of 99%.

A possible technical limitation of current RT-PCR was raised by Fan, Zhang et al. (Chin Med J 2020, see ***below***). The authors evaluated the potential impact of SARS-CoV-2 genome evolution on RT-PCR performance by analysing published primer sets and their match with 77 publicly available whole genome sequences. They found five RT-qPCR primer sets (targeting Orf1ab or N) that may potentially cause false negative results. Targeting the more conserved nsp12 (RdRp) gene was thus recommended.

Tahamtan (Expert Rev Mol Diagn. 2020, see ***below***) provided an overview of the performance issues with RT-PCR. Conclusions were that in case of negative RT-PCR result with clinical features suspicion for COVID-19, especially when

only upper respiratory tract samples were tested, multiple sample types in different time points, including from the lower respiratory tract if possible, should be tested. Combination of real time RT-PCR and clinical features especially CT image could facilitate disease management. Proper sampling procedures, good laboratory practice standard, and using high quality extraction and real-time RT-PCR kit could improve the approach and reduce inaccurate results.

RT-LAMP

Other molecular-based detection techniques include reverse transcription loop-mediated isothermal amplification (RT-LAMP), which feasibility for detection of SARS-CoV-2 has been established by various groups. Isothermal amplification, unlike PCR, enables amplification at a constant temperature using two or three sets of primers and a polymerase with high strand displacement activity, avoiding the need for thermal cycling (Ravi Biosens Bioelectron 2020, see ***below***). To achieve comparable specificity, four different primers are used to amplify six distinct regions on the target gene. As a result, isothermal amplification can achieve higher amounts of nucleic acid copies in a shorter amount of time compared to standard PCR.

Lamb (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.19.20025155v1) demonstrated the feasibility of rapid screening diagnosis completed in under 30 minutes, using Reverse Transcription Loop-Mediated Isothermal Amplification (RT-LAMP) . No validation data have been presented yet. Only simulated patient samples were used, which were created by spiking serum, urine, saliva, oropharyngeal swabs, and nasopharyngeal swabs with a portion of the COVID-19 nucleic sequence.

Yu (Clin Chem 2020, see ***below***) developed an isothermal LAMP based method for COVID-19, amplifying a fragment of the ORF1ab gene. The assay detected synthesized RNA equivalent to 10 copies of virus. Reaction time varied from 15-40 minutes, depending on the loading of virus in the collected samples. 42/43 patient samples initially diagnosed with RTqPCR showed consistent signal after 40 min incubation with the new assay (97.6% sensitivity).

Another LAMP method was described by Baek (Em Micr Inf 2020, see ***below***).

Among the commercially available assays, the ID NOW COVID-19 Test relies on isothermal nucleic acid amplification, targeting a unique region of the RNA-dependent RNA polymerase (RdRP) gene of SARS-CoV-2 (Ravi Biosens Bioelectron 2020, see ***below***). ID NOW COVID-19 Test provides results in 13 minutes or less from throat, nasal or nasopharyngeal swab samples, with reported analytical sensitivity of 125 copies/mL. The ID NOW COVID-19 Test is performed on the ID NOW Instrument, which gives a simple method for mixing sample with test reagents and transferring to the test base through a cartridge.

Another test is Cue Health's Cue COVID-19 Test, a rapid, portable assay that delivers results to a mobile phone in less than 25 minutes. Similar to ID NOW, Cue's test also uses isothermal amplification on nasal swabs, but it detects the SARS-CoV-2 N gene. Additionally, Cue's disposable POC test cartridge forms a connected diagnostic platform with a mobile phone that enables a patient to have convenient access to their health information.

CRISPR-based methods

Several CRISPR-based diagnostic methods have also been described:

- Hou (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.22.20025460v1) reported the development of an isothermal, CRISPR-based diagnostic. The assay demonstrated a near single-copy sensitivity. It was evaluated on 61 specimens with suspected infection (52 positives) and showed great clinical sensitivity with a shorter turn-around time (40 min) than RT-PCR.
- Proof-of-principle of another CRISPR-based detection method was also described by Curti (manuscript on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.02.29.971127v1).
- Broughton (Nat Biotech 2020, see ***below***) reported development of a rapid (<40 min), easy-to-implement and accurate CRISPR-Cas12-based lateral flow assay for detection of SARS-CoV-2 from respiratory swab RNA

extracts. The method was validated using clinical samples from patients in the United States, including 36 patients with COVID-19 infection and 42 patients with other viral respiratory infections. The CRISPR-based DETECTR assay provided a 95% positive predictive agreement and 100% negative predictive agreement compared to the US CDC SARS-CoV-2 real-time RT-PCR assay.

- Javalkote (Methods 2020, see ***below***) presented a compilation of state-of-the-art detection techniques for COVID-19 using CRISPR technology, stating that this approach has tremendous potential to transform diagnostics and epidemiology.

Other molecular methods

Guan (Chin Med J 2020, see ***below***) reported a case with inconsistent fluorescence quantitative-PCR results, for which high-throughput sequencing was used to make a further diagnosis of SARS-CoV-2 infection. Although high-throughput sequencing appears too costly and labour-intensive for routine diagnosis, the authors believe that it can be used for further diagnosis of COVID-19 patients with unclear PCR results under the condition of strict operation and quality control.

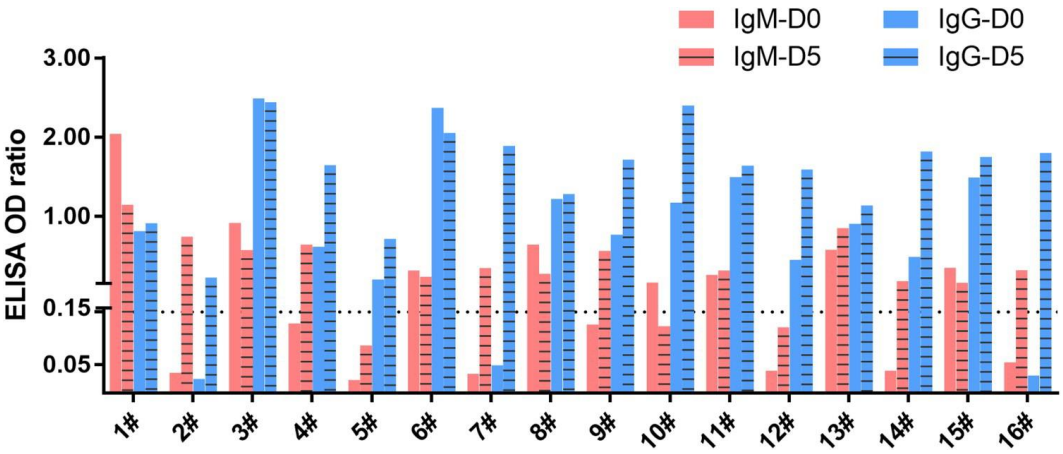
Serological methods

A review paper by Infantino (Isr Med Assoc J 2020, see ***below***) provided an overview on serological diagnostic assays. Bryant (Sci Imm 2020, see below) provided important considerations with regards to use cases of serological assays and implications in terms of assay validation. The review by Pecora (Clin Lab Med 2020, see ***below***) is the most recent summary pertaining to SARS-CoV-2 serology testing. As of today, an impressive number of antibody assays is described (https://www.finddx.org/covid-19/pipeline/?avance=Commercialized&type=all&test_target=Antibody&status=all&section=show-all&action=default).

ELISA

Various ELISA protocols for detection of antibodies to SARS-CoV-2 emerged rapidly, in the first few weeks of the epidemic. For instance, a SARS-CoV-2 IgM and IgG ELISA has been reported by Zhang (Em Micr Inf 2020, see ***below***). The assay is based on recombinant N. A preliminary evaluation was conducted in 16 patients (incl. 3 patients with severe disease). As shown by ***Figure 20***, an increase of specific antibodies was seen in part of the patients as early as by day 5.

Figure 20 Serological detection of SARS-CoV-2. Dashed line indicates cut-off, which was determined based on data from healthy controls (from Zhang Em Micr Inf 2020).



Xiang (manuscript on medRxiv https://www.medrxiv.org/content/10.1101/2020.02.27.20028787v1) reported the evaluation of 2 serological assays: an IgG and IgM ELISA and a colloidal gold-immunochromatographic assay kit for detection of COVID-19. Using 63 samples for the ELISA and 91 plasma samples for the colloidal gold-

immunochromatographic assay, they found a sensitivity of the combined ELISA IgM and ELISA IgG of 55/63 (87.3%), and that of the colloidal gold-immunochromatographic IgM and IgG assay of 75/91 (82.4%). Both methods displayed a specificity of 100%.

Liu (J Clin Micr 2020, see ***below***) reported the evaluation of N and S protein-based IgM and IgG ELISAs in 214 confirmed COVID-19 patients (***Table 11***).

Table 11 IgM and IgG detection in the 214 serum samples from patients with COVID-19 (from Liu J Clin Micr 2020)

No. (%)	positive both rN- and rS- based ELISA	positive only by rN-based ELISA	positive only by rS-based ELISA	negative both rN- and rS-based ELISA
IgM	137(64.0)	9(4.2)	28(13.1)	40(18.7)
IgG	137(64.0)	13(6.1)	22(10.3)	42(19.6)
IgM and/or IgG	162(75.7)	10(4.7)	14(6.5)	28(13.1)

The sensitivity of the S-based ELISA for IgM detection was found significantly higher than that of the N-based ELISA. An increase in the sensitivity of IgM and IgG detection was observed with an increasing number of days post-disease onset. The positive rate of N-based and S-based IgM and IgG ELISAs was less than 60% during the early stage of the illness (day 0-10), and increased after 10 days.

A study by Zhao (Clin Inf Dis 2020, see ***below***) investigated the dynamics of total Ab, IgM and IgG antibody against SARS-CoV-2 in serial blood samples collected from 173 confirmed COVID-19 patients. Testing was performed ELISA kits supplied by Beijing Wantai Biological Pharmacy Enterprise. Antibodies were found in <40% of patients within 1-week since onset, and rapidly increased to 100.0% (Ab), 94.3% (IgM) and 79.8% (IgG) by day-15 after onset. In contrast, RNA detectability decreased from 66.7% (58/87) in samples collected before day-7 to 45.5% (25/55) between day 15 and 39. Combining RNA and antibody detections significantly improved the sensitivity of pathogenic diagnosis for COVID-19.

Okba (Em Inf Dis 2020, see ***below***) presented validation data for in house S and N based ELISAs as well as for a β version of the Euroimmun commercial S1 IgG or IgA ELISAs. In the 3 in-house ELISAs tested, the RBD and N protein ELISAs were more sensitive than S1 ELISA in detecting antibodies in mildly infected patients and showed stronger correlations with PRNT50 titers. Therefore, the authors indicated that detecting antibodies against 2 different antigens might be needed to avoid false-negative results in surveillance studies.

Wang (J Clin Microb 2020, see ***below***) reported that middle-high level of rheumatoid factor-IgM in sera could lead to false-positive reactivity in SARS-CoV-2 IgM GICA (colloidal gold immunochromatography assay) and ELISA assays. The authors suggested that urea dissociation tests would be helpful in reducing such false-positive SARS-CoV-2 IgM results.

Hicks (manuscript on medRxiv : https://doi.org/10.1101/2020.06.22.20137695) evaluated the serologic reactivity of pre-pandemic archival blood serum samples (pre2019) and samples collected in April 2020 in the US (New York and New Jersey) from a community highly affected by SARS-CoV-2. Utilizing twelve previously reported ELISAs, the authors tested IgG, IgM and IgA reactivity against S proteins from SARS-CoV-2, MERS-CoV, SARS-CoV, HCoV-OC43, and HCoV-HKU1. They detected the potential cross-reactivity of antibodies against SARS-CoV-2 towards the four other coronaviruses, with the strongest cross-recognition between SARS-CoV-2 and SARS /MERS-CoV antibodies. They advised that the interpretation of current serological results should take into account archival patient sera (pre2019), including sera from known SARS-CoV and MERS convalescent patients, to properly analyse the resulting data and adjust any estimates of seropositivity as needed.

Of note, Stadlbauer (Curr Protoc Microbiol 2020, see ***below***) described a detailed protocol for expression of antigens derived from the S protein of SARS-CoV-2 that can serve as a substrate for immunological assays, as well as the protocol of a two-stage ELISA.

Chemiluminescence (CLIA)

Jin (Int J Infect Dis 2020, see ***below***) investigated the diagnostic value of serological test and evolution of test results over time in 43 COVID-19 patients. SARS-CoV-2 IgM and IgG chemiluminescence immunoassay (CLIA) kits from Shenzhen YHLO Biotech Co., Ltd (China) were used, with two antigens of SARS-CoV-2 coated on the magnetic beads of these CLIA assays (N and S proteins). Compared to molecular test, the sensitivity of serum IgM and IgG antibodies to diagnose COVID-19 was 48.1% and 88.9%, and the specificity was 100% and 90.9%. However, IgG positive rate increased till 100% over time.

Padoan (Clin Chem Lab Med 2020, see ***below***) and Lippi (Clin Chem Lab Med 2020, see ***below***) reported on the validation of MAGLUMI 2000 Plus CLIA assay for the measurement of specific IgM and IgG in sera. Results of MAGLUMI IgM and IgG were well aligned with those of Euroimmun Anti-SARS-CoV-2 IgA and IgG, especially concerning the IgG and the cumulative immunoglobulin profile.

Pseudotype neutralization assay

Nie (Emerg Microbes Infect 2020, see ***below***) reported on a pseudovirus neutralization assay for SARS-CoV-2 and its validation. The assay is based on a VSV pseudovirus system. The key parameters for this assay were optimized, including cell types, cell numbers, virus inoculum. With this test, SARS-CoV-2 convalescent patient sera showed high neutralizing potency. The assay showed relatively low coefficient of variations with 15.9% and 16.2% for the intra- and inter-assay analyses respectively.

Rapid test for antibody detection

Li, Yi et al. (J Med Vir 2020, see ***below***) reported the development of a rapid and simple point-of-care lateral flow SARS-CoV-2 immunoassay which can detect IgM and IgG antibodies simultaneously in human blood within 15 minutes. The clinical detection sensitivity and specificity of this test were measured using blood samples collected from 397 PCR-confirmed COVID-19 patients and 128 negative patients at 8 different clinical sites. The overall testing sensitivity reached 88.66% and specificity 90.63%. The assay was evaluated on fingerstick blood samples, as well as serum and plasma from venous blood.

In March 2020, Cassaniti (J Med Vir 2020, see ***below***) reported a study aimed at validating the VivaDiagTM COVID-19 IgM/IgG Rapid Test lateral flow immunoassay (LFIA) for the rapid diagnosis of COVID-19, in real-life conditions. The performance of VivaDiagTM COVID-19 test was assessed in 50 patients at their first access at emergency room department with fever and respiratory syndrome in comparison with results of nasal swab molecular screening. Sensitivity of the VivaDiagTM COVID-19 IgM/IgG Rapid Test was only 18.4%, specificity was 91.7%, while NPV was 26.2% and PPV was 87.5% in patients enrolled from emergency room department. The assay could thus not be recommended for triage of suspect patients.

Pan (J Inf 2020, see ***below***) compared an immunochromatographic strip assay targeting viral IgM or IgG antibody (Zhuhai Livzon Diagnositic Inc.) to RT-PCR. The sensitivity of ICG assay with IgM and IgG combinatorial detection in nucleic acid confirmed cases were 11.1%, 92.9% and 96.8% at the early (1-7 days after onset), intermediate (8-14 days after onset), and late stage (more than 15 days), respectively. The ICG detection capacity in nucleic acid-negative suspected cases was 43.6%.

Performance of serological testing

Early in the pandemic, lack of regulatory restrictions on serologic testing led to a wave of more than 40 antibody tests to detect immunoglobulin (Ig) G and/or IgM binding to SARS-CoV-2 S and N. Many of these tests were poorly

characterized, which caused concern about the quality of serologic data (Pecora Clin Lab Med 2020, see ***below***). The US FDA then moved to tighten regulation of new commercial serologic tests; more than 30 were subsequently withdrawn from distribution. These events highlighted the importance of rigorous testing evaluation and scope of use.

A Cochrane review assessed the performance of serological assays (Deeks Cochrane Database Syst Rev 2020, see ***below***). The authors concluded that the sensitivity of antibody tests is too low in the first week since symptom onset to have a primary role for the diagnosis of COVID-19, but that these assays may still have a role complementing other testing in individuals presenting later, when RT-PCR tests are negative, or are not done. Antibody tests are likely to have a useful role for detecting previous SARS-CoV-2 infection if used 15 or more days after the onset of symptoms. However, the duration of antibody rises is currently unknown, and very little data was found beyond 35 days post-symptom onset, leading to uncertainty about the utility of these tests for seroprevalence surveys. Concerns about high risk of bias and applicability made it likely that the accuracy of tests when used in clinical care will be lower than reported in published studies. Sensitivity has mainly been evaluated in hospitalised patients, so it is unclear whether the tests are able to detect lower antibody levels likely seen with milder and asymptomatic COVID-19. The design, execution and reporting of studies of the accuracy of COVID-19 tests was found to require considerable improvement.

Rapid test for antigen detection

Numerous commercial assays are now available for SARS-CoV-2 antigen detection (https://www.finddx.org/covid-19/pipeline/?avance=Commercialized&type=all&test_target=Antigen&status=all&section=show-all&action=default). The performance of rapid tests for antigen detection was analysed by Dinnes (Cochrane Database Syst Rev 2020, see ***below***). This review identified early-stage evaluations of point-of-care tests for detecting SARS-CoV-2 infection, largely based on remnant laboratory samples. The findings currently have limited applicability, as it is uncertain whether tests will perform in the same way in clinical practice, and according to symptoms of COVID-19, duration of symptoms, or in asymptomatic people. The sensitivity of rapid antigen tests varied considerably across studies (from 0% to 94%): the average sensitivity was 56.2% (95% CI 29.5 to 79.8%) and average specificity was 99.5% (95% CI 98.1% to 99.9%; based on 8 evaluations in 5 studies on 943 samples). Data for individual antigen tests were limited with no more than two studies for any test. The authors concluded that rapid tests have the potential to be used to inform triage of RT-PCR use, allowing earlier detection of those testing positive, but the evidence currently is not strong enough to determine how useful they are in clinical practice. Prospective and comparative evaluations of rapid tests for COVID-19 infection in clinically relevant settings are urgently needed.

Chest CT for COVID-19 detection

Chest CT soon emerged as an alternative approach to COVID-19 diagnosis. Fang (Radiol 2020, see ***below***) reported, for instance, that in a series of 81 patients, the sensitivity of chest CT was found greater than that of RT-PCR (98% vs 71%, respectively, p<.001). In that early study, subjects with initial negative RT-PCR became positive upon retest 1 to 7 days later. These results provided first evidence of a possible role for chest CT for screening patients with clinical and epidemiologic features compatible with COVID-19 particularly when RT-PCR testing is negative.

Ai (Radiol 2020, see ***below***) reported a large study further supporting the diagnostic value of chest CT. Of 1014 patients included in the study, 59% had positive RT-PCR results, and 88% had positive chest CT scans. The sensitivity of chest CT in suggesting COVID-19 was 97% based on positive RT-PCR results. In patients with negative RT-PCR results, 75% (308/413) had positive chest CT findings; among them, 48% were considered as highly likely cases, 33% as probable cases. The mean interval time between the initial negative to positive RT-PCR results was 5.1 ± 1.5 days. Moreover, 60% to 93% of cases had initial positive CT consistent with COVID-19 prior (or parallel) to the initial positive RT-PCR results. Interestingly, 42% (24/57) cases showed improvement in follow-up chest CT scans before the RT-PCR results turning negative.

A meta-analysis by Kim (Radiology 2020, see ***below***), based on 68 publications, assessed the diagnostic performance of chest CT and RT-PCR. The pooled sensitivity was 94% (95% CI: 91%, 96%; I2=95%) for chest CT and 89% (95% CI: 81%, 94%; I2=90%) for RT-PCR. The pooled specificity was 37% (95% CI: 26%, 50%; I2=83%) for chest CT. For chest CT scans, the positive predictive value (PPV) ranged from 1.5% to 30.7%, and the negative predictive value (NPV) ranged from 95.4% to 99.8%. For RT-PCR, the PPV ranged from 47.3% to 96.4%, while the NPV ranged from 96.8% to 99.9%. The sensitivity of CT was affected by the distribution of disease severity, the proportion of patients with comorbidities, and the proportion of asymptomatic patients (all $p < 0.05$). Interestingly, the sensitivity of RT-PCR was negatively associated with the proportion of elderly patients ($p = 0.01$).

Several researchers developed artificial intelligence systems to interpret CT images. These are discussed in the ***Clinical prediction models*** section above.

Combination of chest CT and RT-PCR

A publication in Lancet (Shi Lancet Inf Dis 2020, see ***below***), which presented clinical imaging data from a cohort of 81 patients, stated that combining imaging assessments with clinical and laboratory findings could help identify SARS-CoV-2 infections early. A similar conclusion was reached by Ren (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.25.20027755v2) based on 87 confirmed COVID-19 cases and 481 exclusion cases. Combination of RT-PCR and CT had higher sensitivity (91.9%) than RT-PCR alone (78.2%) or CT alone (66.7%) or combination of two RT-PCR tests (86.2%).

Virus isolation

The first SARS-CoV-2 was successfully isolated by inoculating human airway epithelial cells with bronchoalveolar-lavage fluid samples from a patient with pneumonia (Zhu NEJM 2020, see ***below***). Since human airway epithelial cells (because of their resemblance to pseudostratified mucociliary epithelium) require 4-6 weeks to differentiate *in vivo*, isolation of SARS-CoV-2 using Vero cells or Caco-II cells is more convenient. Kim (Osong Public Health Res Perspect 2020, see ***below***) showed virus replication in Vero cells, with cytopathic effects observed. The author indicated that further studies are needed to select more sensitive cell lines suitable for virus isolation from low viral load samples. Harcourt (Em Inf Dis 2020, see ***below***) presented data showing that the virus replicates to high titer in Vero-CCL81 cells and Vero E6 cells in the absence of trypsin.

Matsuyama (PNAS 2020, see ***below***) showed that a TMPRSS2-expressing Vero E6 cell line is highly susceptible to SARS-CoV-2 infection, making it useful for isolating and propagating the virus.

Alternative diagnostic methods

Various alternative approaches to COVID-19 diagnosis have been reported. For instance, a manuscript by Wang (on arXiv: https://arxiv.org/abs/2002.05534) described the development of a technology for detection of abnormal respiratory patterns for large-scale screening of COVID-19 patients in an unobstructive manner.

Seo (ACS Nano 2020, see ***below***) reported a field-effect transistor (FET)-based biosensing device for detecting SARS-CoV-2 in clinical samples. This type of device has several advantages, including the ability to make highly sensitive and instantaneous measurements using small amounts of analytes. The sensor was produced by coating graphene sheets of FET with a specific antibody against SARS-CoV-2 spike protein. The performance of the sensor was determined using antigen protein, cultured virus, and nasopharyngeal swab specimens from COVID-19 patients. The FET device could detect SARS-CoV-2 S protein at concentrations of 1 fg/ml in PBS and 100 fg/ml clinical transport medium. In addition, the FET sensor successfully detected SARS-CoV-2 in culture medium (limit of detection [LOD]: 1.6×10^1 pfu/ml) and clinical samples (LOD: 2.42×10^2 copies/ml). The device exhibited no measurable cross-reactivity with MERS-CoV antigen. Even though more validation data are needed, these results appear very promising.

The sweat produced by SARS-CoV-2 PCR-positive individuals may have a different odour for trained detection dogs than the sweat produced by non-PCR-positive persons. A proof-of-concept study by Grandjean (manuscript on bioRxiv : https://doi.org/10.1101/2020.06.03.132134) tested this hypothesis on a total of 198 armpit sweat samples obtained from different hospitals (3 sites). For each dog, the acquisition of the specific odour of SARS-CoV-2 sweat samples required from one to four hours, with a number of positive samples sniffing ranging from 4 to 10. They kept 8 dogs of the initial group (explosive detection dogs and colon cancer detection dogs), who performed a total of 368 trials. The success of the dogs in finding positive sample in a line containing several negative samples or mocks (2 to 6) were 100% for 4 dogs, and respectively 83%, 84% and 94% for the others. They conclude that there is a very high evidence that the armpit sweat odour of SARS-CoV-2 positive individuals is different, and that dogs can detect a person infected by SARS-CoV-2.

Similarly, Vesga (manuscript on bioRxiv: https://doi.org/10.1101/2020.06.17.158105) trained six dogs to identify the scent-mark of SARS-CoV-2 using respiratory secretions obtained from COVID-19 patients confirmed by RT-PCR. The initial training phases took 28 days for in vitro recognition and 21 days for in vitro diagnosis of SARS-CoV-2, during which time the dogs scent-interrogated 3,200 and 6,000 samples, respectively. As a group, the six dogs achieved overall diagnostic accuracy of 99.6%, diagnostic sensitivity of 95.5% (95% CI 90.4–97.9%), specificity of 99.6% (95% CI 99.5–99.8%), and positive and negative predictive values of 85.7% (95% CI 79.2–90.5%) and 99.9% (95% CI 99.8–100.0%) with a mean testing population prevalence of 2.2%. The next phase, in which the dogs will be exposed to humans for diagnosis of COVID-19, is reportedly ongoing.

Jendrny trained eight detection dogs were for 1 week to detect saliva or tracheobronchial secretions of SARS-CoV-2 infected patients in a randomised, double-blinded and controlled study (BMC Inf Dis 2020, see ***below***). The dogs were able to discriminate between samples of infected (positive) and non-infected (negative) individuals with average diagnostic sensitivity of 82.63% (95% confidence interval [CI]: 82.02–83.24%) and specificity of 96.35% (95% CI: 96.31–96.39%). During the presentation of 1012 randomised samples, the dogs achieved an overall average detection rate of 94% (±3.4%) with 157 correct indications of positive, 792 correct rejections of negative, 33 incorrect indications of negative or incorrect rejections of 30 positive sample presentations.

Prevention and control strategies

Human disease surveillance guidelines

WHO issued guidance on implementation of global surveillance of COVID-19 by Member States (https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov), last updated on August 7 2020). The objectives of this global surveillance were to monitor trends of the disease where human to human transmission occurs; rapidly detect new cases in countries where the virus is not circulating; provide epidemiological information to conduct risk assessments at the national, regional and global level; and provide epidemiological information to guide preparedness and response measures.

Recommendations for laboratory testing

Any persons meeting the criteria for testing should be tested for COVID-19 infection. Depending on the intensity of transmission, the number of cases and laboratory testing and surge capacity, it may be necessary to prioritize who gets tested. A WHO guidance (dated March 21st) is available to help define such priorities (https://apps.who.int/iris/bitstream/handle/10665/331509/WHO-COVID-19-lab_testing-2020.1-eng.pdf). The document focusses solely on molecular testing.

Recommendations for reporting surveillance data to WHO

WHO requested that national authorities report probable and confirmed cases of novel coronavirus infection within 24 hours of identification, by providing the minimum data set outlined in the "Interim case reporting form for 2019 Novel Coronavirus of confirmed and probable cases"(https://www.icao.int/safety/CAPSCA/PublishingImages/Pages/Coronavirus/WHO%2020200121-2019-ncov-reporting-form.pdf). For countries with extensive importation or human-to-human transmission, daily aggregated data were requested, with reporting of the number of new confirmed and probable cases and deaths by first administrative level (e.g. region, province, state, municipalities) if possible. Of note, in a press conference on Feb 4, WHO mentioned they only received complete information about 38% of the cases reported outside of China (https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-technical-briefing-on-2019-novel-coronavirus).

Surveillance in animal populations

Approaches to testing of Companion Animals of COVID-19 patients

Reports from Hong Kong soon suggested that authorities routinely quarantined and tested companion animals owned by COVID-19 patients (ProMed-mail, Archive Number: 20200403.7179945, https://promedmail.org/promed-post/?id=20200403.7179945). In March 2020, the US CDC reported that they are applying an *ad hoc* approach to the testing of pets belonging to human COVID-19 patients in the USA. This is being done on a case by case basis according to a risk assessment (OIE, https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/3rd_call_OIE_informal_advisory_group_on_COVID19_and_animals.pdf). The minutes of the 4th meeting of the OIE Advisory Group on COVID-19 stated that 'FAO have informed the OIE that some laboratories in Italy are preparing to test pets. No routine testing of pets has been reported in other European countries, although in Germany any animal that shows respiratory disease symptoms and has had contact with a COVID-19 positive human is eligible for testing'. (OIE, https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/4th_call_OIE_informal_advisory_group_on_COVID19_and_animals.pdf).

In April 2020, IDEXX Laboratories have reported testing more than 5000 specimens from dogs, cats and horses with respiratory disease in more than 17 countries (in North America, Europe and Asia) with their SARS-CoV-2 (COVID-19) RealPCR Test since 14th February (IDEXX, https://www.idexx.com/en/about-idexx/news/idexx-makes-pet-test-covid-19-virus-available-veterinarians/; IDEXX, https://www.idexx.com/en/veterinary/reference-laboratories/coronavirus-diagnostic-update/). Over 3500 of these samples had been sourced from the USA (all 50 states) and South Korea. Areas with high community transmission at the time of sample collection (such as Seattle) were represented. 55% of specimens were canine, 41% were feline and 4% were equine; 77% were respiratory samples (mostly deep pharyngeal and conjunctival), 23% were faecal samples. Specimens were also tested in parallel with 3 assays from the CDC. No samples tested positive. Detailed metadata regarding sample type and location is not available. In the report, IDEXX stated 'Our monitoring of canine and feline specimens submitted for diagnostic respiratory RealPCR panels is ongoing and has now expanded to Canada, all US states, and countries within the EU, including areas with high rates of COVID-19 in the human population'.

Surveillance studies in animal populations

Temmam (One Health 2020, see ***below***) reported a study in which they tested 21 domestic animals (9 cats and 12 dogs) belonging to members of a veterinary student community in which 11/18 students had clinical signs consistent with COVID-19 (including fever, cough, anosmia etc) and 2 tested positive to SARS-CoV-2 by RT-PCR. Whilst 3 cats displayed clinical signs consistent with coronavirus disease (respiratory or digestive signs), no pet tested positive for SARS-CoV-2 by RT-PCR on nasal and rectal swabs and no animals demonstrated an antibody response when screened with an immunoprecipitation assay.

Mallapaty (Nature 2020, see ***below***) discussed data from a manuscript on a preprint server showing that cats can be infected by SARS-CoV-2 in experimental conditions, and develop antibodies against the virus in the absence of disease symptoms. Virus transmission was observed in 1/3 cats exposed to infected animals. Dogs were not found to excrete infectious virus, and investigations in pigs, chickens and ducks identified no viral RNA in inoculated animals. Overall, none of these species is thought to play a part in the epidemiology of COVID-19. Halfmann (New Eng J Med, 2020, see ***below***) experimentally evaluated the nasal shedding of SARS-CoV-2 from inoculated cats and the subsequent transmission to cats with no previous infection with the virus. Despite the low sample size (n=3), SARS-COV-2 was detected in nasal swab specimens of all healthy cohoused cats 3 to 6 days post-exposure to the infected cat. Cats showed no symptoms, including abnormal body temperature, substantial weight loss or conjunctivitis. All the animals had IgG antibody titers between 1:5120 and 1:20480 on day 24 after the initial inoculation. The authors emphasized the fact that cats may be silent intermediate host of SARS-CoV-2. This is supported by the results of Gaudreault (manuscript on bioRxiv : https://doi.org/10.1101/2020.08.04.235002) who found that asymptomatic cats can be productively infected and readily transmit SARS-CoV-2 (USA-WA1/2020 strain) to other susceptible cats. The ease of transmission between domestic cats indicates a significant public health necessity to investigate the potential chain of human-cat-human transmission. Moreover, SARS-CoV-2 RNA was detected in nasal swabs of the principal infected cats at 1 through 10 days post challenge (DPC), with maximal quantities observed from 1 through 5 DPC. The nasal swabs of contact animals became RNA positive for SARS-CoV-2 starting at day 2 post contact (i.e. 3 DPC) and remained positive up to 9 days post contact/10 DPC, with a maximum on day 6 post contact/7 DPC that is nearly as high as the copy number detected in the principal infected animals at 1 through 5 DPC. These findings warrant COVID-19 screening of felines for surveillance/epidemiological purposes and for implementing of mitigation strategies; they also point towards nasal swabs/washes and rectal swabs as appropriate diagnostic samples. High viral RNA levels were detected throughout nearly all tissues tested for all cats at 4 and 7 DPC, with reduced levels or clearing by 21 DPC in some tissues: residual RNA was detected mainly in the upper respiratory tract, the lymphoid tissues and the CNS. Since no virus was detected in blood, it remains to be studied how the virus reaches and infects non-respiratory tissues. The detection of high levels of viral RNA from swab samples and in various organs and tissues, along with mild to moderate histologic changes in trachea and bronchi associated with viral RNA and viral antigen, and the development of SARS-CoV-2-specific antibodies demonstrates that cats were productively infected, without developing any obvious clinical signs. As such, cats may thus serve as potential models for asymptomatic COVID-19 infections in humans.

China reported to the OIE on 5th February 2020 that veterinary departments 'had carried out 2019-nCoV testing towards samples of pigs, poultry and dogs and other domestic animals collected since 2019 (mainly in late 2019). So far, results of such testing are all negative.' ProMED mail and OIE meeting minutes indicate that prior to 9th February, the China Animal Health Epidemiology Center (CAHEC) tested over 4800 archived animal samples (including samples from poultry, cat, dogs and pigs) that had been collected in 2019 in numerous locations around China. There is no indication that these samples included animals known or suspected to be exposed to COVID-19 infected people. SARS-CoV-2 was not detected in any samples. Further reports indicated that 'animals from fur farms (including mink, foxes, raccoon dogs) had been tested for SARS-CoV-2 by RT-PCR' and found negative. (ProMED-mail, Archive Number: 20200220.7009213, https://promedmail.org/promed-post/?id=7009213; OIE, https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/China_update_COVID-19.pdf; OIE, https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/COV-19/4th_call_OIE_informal_advisory_group_on_COVID19_and_animals.pdf).

Zhang (manuscript on bioRxiv: http://biorxiv.org/content/early/2020/04/03/2020.04.01.021196.abstract) reported results of a serosurveillance study performed on a cohort of feline serum samples in the Wuhan region prior to and during the outbreak. 15 of 102 (14.7%) cat sera collected after the outbreak were positive for antibody to the RBD of SARS-CoV-2 by indirect ELISA. Among the positive samples, 11 had SARS-CoV-2 neutralizing antibodies with a titer ranging from 1/20 to 1/1080. No serological cross-reactivity was detected between the SARS-CoV-2 and type I or II

feline infectious peritonitis virus (FIPV). The data demonstrated that SARS-CoV-2 has infected cat population in Wuhan during the outbreak. Of note, there was very limited information provided in the paper regarding the sampling strategy applied to the surveillance. Some of the animals were reported to be pets of COVID-19 patients, whilst others are stray cats and those from pet hospitals. All animals in the study were reported to have had nasopharyngeal and rectal swabs collected at the time of sampling, and all swabs tested negative on a SARS-CoV-2 specific qRT-PCR using a commercial kit which targeted ORF1ab and N genes.

Deng (Transbound Emerg Dis 2020, see ***below***) performed a serological survey of on 1914 serum samples from 35 animal species in (including pigs, cows, sheep, horses, chickens, ducks, geese, experimental mice, rats, guinea pigs, rabbits, monkeys, dogs, cats, wild camels, foxes, minx, alpacas, ferrets, bamboo rats, peacocks, eagles, tigers, rhinoceroses, pangolins, leopard cats, jackals, giant pandas, masked civets, porcupines, bears, yellow-throated martens, weasels, red pandas and wild boar) using a double-antigen sandwich ELISA, with no positive results. Importantly, positive ELISA results were not reported among 15 pet and 99 street dogs from Wuhan. Otherwise, there was very limited information presented regarding the animal populations from which the samples were derived.

An indirect multi-species ELISA based on the RBD of SARS-CoV-2 was made available to support animal studies. The assay was validated using 59 sera of infected or vaccinated animals including ferrets, raccoon dogs, hamsters, rabbits, chickens, cattle and a cat, and a total of 220 antibody-negative sera of the same animal species. Overall, a diagnostic specificity of 100.0% and sensitivity of 98.31% was achieved. This test (based on two markers SARS-CoV-2 S1 and the RBD-SD1 domain) enabled high-throughput antibody detection in a broad range of animal species, which may be used for outbreak investigations, to assess the seroprevalence in susceptible species or to screen for reservoir or intermediate hosts (Wernike, on bioRxiv : https://doi.org/10.1101/2020.08.26.266825).

Overview of public health responses

Public health response in China

As of 26 January 2020, in China, 30 provinces initiated a level-1 public health response to control COVID-19. As described by Deng (J ClinMed 2020, see ***below***), level-1 response means that during the occurrence of a particularly serious public health emergency, the provincial headquarters shall organize and coordinate the emergency response work within its administrative area according to the decision deployment and unified command of the State Council. Fever observation rooms were to be set up at stations, airports, ports, and so on to detect the body temperature of passengers entering and leaving the area and implement observation/registration for the suspicious patients. The government under its jurisdiction, in accordance with the law, is to take compulsory measures to restrict all kinds of the congregation, and ensure the supply of living resources. They also ensure the sufficient supply of masks, disinfectants, and other protective articles on the market, and standardize the market order. The strengthening of public health surveillance, hygiene knowledge publicity, and monitoring of public places and key groups is required. Comprehensive medical institutions and some specialized hospitals are to be prepared to accept COVID-19 patients to ensure that severe and critical cases can be differentiated, diagnosed, and effectively treated in time. The health administration departments, public health departments, and medical institutions at all (province, city, county, district, township, and street) levels, and social organizations function in epidemic prevention and control and provide guidance for patients and close contact families for disease prevention.

Chen, Yang et al. (Lancet 2020, see ***below***) also underlined the importance of the social distancing measures that were applied during the Chinese Lunar New Year holiday in China. People in China are indeed estimated to make close to 3 billion trips over the 40-day travel period, or Chunyun, of the Lunar New Year holiday. As part of these social distancing policies, the Chinese Government encouraged people to stay at home; discouraged mass gatherings; cancelled or postponed large public events; and closed schools, universities, government offices, libraries, museums, and factories. Only limited segments of urban public transport systems remained operational and all cross-province bus routes were

taken out of service. As a result of these policies and public information and education campaigns, Chinese citizens started to take measures to protect themselves against COVID-19, such as staying at home as far as possible, limiting social contacts, and wearing protective masks when they needed to move in public. The Chinese Government even extended the Lunar New Year holiday, so that the duration of the holiday would be sufficiently long to fully cover the suspected incubation period of COVID-19.

China took draconian measures to contain the outbreak, including the quarantine of at least 30 million residents of Wuhan and neighbouring cities (Kickbusch British Med J 2020, see ***below***). Countrywide interventions include delaying resumption of school after the spring festival holiday, encouraging citizens to work from home and stay at home, using personal protective equipment such as face masks, and cancelling all mass gatherings. Vehicular traffic in Wuhan was banned. Authorities closed public transit and cancelled outbound transportation (air, train, and long-haul buses). China also imposed a ban on overseas travel with tour groups and suspended sale of flight and hotel packages. Authorities cancelled Lunar New Year gatherings in Beijing as well as intraprovince bus service into the nation's capital. China's Finance Ministry announced ¥1 billion (U.S. $145 million) to fund the response as well as the rapid construction of 2 hospitals in Wuhan to treat those affected (Phelan JAMA 2020, see ***below***).

Most districts of Hangzhou announced in a statement that every community would be kept under closed management, and only one family member was allowed to leave his house and buy daily living supplies outdoors every two days (Diao Infect Control Hosp Epidemiol 2020, see ***below***). Furthermore, "non-contact delivery", a new delivery method, was adopted by many express delivery companies, which could reduce contagion risk. Fourth, in order to reduce the concentration of personnel to avoid the risk of cross-infection, online working and network teaching were encouraged for workers and students, respectively, which were supported by mobile technology companies. Fifth, to meet the need of resumption of production and curb the transmission of the virus as far as possible, Hangzhou arranged chartered transportation to help numbers of migrants return to workplaces. Lastly, in cooperation with Alipay, Hangzhou adopted the health QR code system on February 11, 2020, which were designated by green, yellow or red. People who wanted to get into Hangzhou needed to submit their travel history and health information online in advance. Residents with a green code indicated they had a low current risk of being infected, while residents with yellow or red codes were quarantined for seven or fourteen days and required to report their health condition every day to exclude infection before the codes turned green.

The strong public health response in China could not prevent the spread of COVID-19 to other countries, causing a worldwide public health crisis. Shangguan (Int J Environ Res Public Health 2020, see ***below***) analysed the various reasons why China could not contain the outbreak. The authors suggested that the country should adopt a Singaporean-style public health crisis information management system to ensure information disclosure and information symmetry and should use it to monitor public health crises in real time. They added that the central government should adopt the territorial administration model of a public health crisis and increase investment in public health in China.

Public health response in other countries

The first COVID-19 case outside China is said to have been reported on January 13 2020: a patient in Thailand was said to have visited the Huanan Seafood Wholesale Market (Bruinen de Bruin Saf Sci 2020, see ***below***). Due to the absence of a cure or a vaccine, controlling the infection to prevent the spread of COVID-19 was correctly seen as the only intervention that could be used. Risk mitigation measures were soon implemented on other areas and countries such as Hong Kong, Taiwan, South Korea and Mongolia. One of them consisted of contact tracing and recommending a set of precautions. In the United States, on January 20, state and local health departments, in collaboration with teams deployed from CDC, began identifying and monitoring all persons considered to have had close contact with patients with confirmed COVID-19 (Burke MMWR Morb Mortal Wkly Rep 2020, see ***below***). The aims of these efforts

were to ensure rapid evaluation and care of patients, limit further transmission, and better understand risk factors for transmission.

Tanne, Hayasaki et al. (BMJ 2020, see ***below***) provided a rapid overview of how selected countries (USA, Canada, Australia, India, Japan, South Korea, Italy, Spain, France, Germany, Iran) were tackling the epidemic in March 2020).

Hong Kong declared its highest-tier emergency, curtailed public events, and barred travellers from Hubei Province. Travelers from mainland China had to complete health declarations. Hong Kong has also rapidly closed schools and universities. Governments have not banned travel from China, with 2 exceptions: North Korea prohibited entry of all Chinese travellers and Kyrgyzstan closed its border with China. Multiple countries (e.g., Australia, Thailand, South Korea, Japan, India, Italy, Singapore, Malaysia, and Nigeria) implemented temperature screening, symptom screening, and/or questionnaires for arriving passengers from China. The U.S. Centers for Disease Control and Prevention launched enhanced, non-invasive screening of travellers from Wuhan at 20 major airports, while the U.S. State Department issued its highest-level travel advisory for Hubei Province: level 4, "do not travel."

Legido-Quigley (Lancet 2020, see ***below***) analysed the response in Hong Kong, Singapore and Japan. The three locations introduced appropriate containment measures and governance structures; took steps to support health-care delivery and financing; and developed and implemented plans and management structures. However, their response was found vulnerable to shortcomings in the coordination of services; access to adequate medical supplies and equipment; adequacy of risk communication; and public trust in government. Three important lessons emerged. The first is that integration of services in the health system and across other sectors amplifies the ability to absorb and adapt to shock. The second is that the spread of fake news and misinformation constitutes a major unresolved challenge. Finally, the trust of patients, health-care professionals, and society as a whole in government is of paramount importance for meeting health crises.

The response of Singapore to contain the epidemic was also described in a publication by Lee (J Trav Med 2020, see ***below***).

From January 30, the Italian Government implemented extraordinary measures to restrict viral spread, including interruptions of air traffic from China, organised repatriation flights and quarantines for Italian travellers in China, and strict controls at international airports' arrival terminals (Spina Lancet 2020, see ***below***). Local medical authorities adopted specific WHO recommendations to identify and isolate suspected cases of COVID-19. Such recommendations were addressed to patients presenting with respiratory symptoms and who had travelled to an endemic area in the previous 14 days or who had worked in the health-care sector, having been in close contact with patients with severe respiratory disease with unknown aetiology. Suspected cases were transferred to preselected hospital facilities where the SARS-CoV-2 test was available and infectious disease units were ready for isolation of confirmed cases. Since the first case of SARS-CoV-2 local transmission was confirmed, the Emergency Medical System in the Lombardy region (reached by dialling 112, the European emergency number) represented the first response to handling suspected symptomatic patients, to adopting containment measures, and to addressing population concerns. The Emergency Medical System of the metropolitan area of Milan instituted a COVID-19 Response Team of dedicated and highly qualified personnel, with the ultimate goal of tackling the viral outbreak without burdening ordinary activity. More details on the consequences of the COVID-19 outbreak on critical care capacity were provided by Grasselli (JAMA 2020, see ***below***).

Johnson (Euro Surv 2020, see ***below***) characterised three sequential scenarios for the spread of SARS-CoV-2 in the EU/EEA, with the third scenario divided in two sub-scenarios based on impact on the healthcare system. The scenarios were: (1) short, sporadic chains of transmission, (2) localised sustained transmission, (3a) widespread sustained transmission with increasing pressure on the healthcare system and (3b) widespread sustained transmission with

overburdened healthcare system. These scenarios were presented together with suggested control measures to limit the impact of the epidemic. At different points in time, it was expected that different countries may find themselves in different scenarios.

Bruinen de Bruin (Saf Sci 2020, see ***below***) collated and clustered (using harmonised terminology) the risk mitigation measures taken around the globe in the combat to contain, and since March 11 2020, to limit the spread of the SARS-CoV-2 virus. ***Figure 21*** describes the timeline of events up to end of March 2020.

Figure 21 Time line of events and application of COVID-19 risk mitigation measures (from Bruinen de Bruin Saf Sci. 2020)

A WHO report dated August 20 2020 provided information on pandemic preparedness and response in Malaysia (https://www.who.int/publications/m/item/malaysia-strong-preparedness-and-leadership-for-a-successful-covid-19-response). Another report issued on September 30 2020 described how the strong health system in Thailand fights the pandemic (https://www.who.int/publications/m/item/thailand-how-a-strong-health-system-fights-a-pandemic).

Of note, a convenient platform has been created for access to detailed information on how different countries respond to the pandemic (see: https://www.covid19healthsystem.org/mainpage.aspx).

Infection control in health care settings

As reported by Wang (J Hosp Inf 2020, see ***below***), by 24th February, the National Health Commission of the People's Republic of China reported in a press conference of WHO-China Joint Mission on COVID-19 that 3 387 healthcare workers had been confirmed with COVID-19, with 22 (0.6%) deaths. More than 90% of infected HCWs were from Hubei province. The director of National Hospital Infection Management and Quality Control Centre summarized some reasons for such high number of infected HCWs during emergency outbreak. These included inadequate personal protection of HCWs at the beginning of the epidemic; long-time exposure to large-scale of infected patients, which directly increased the risk of infection for HCWs; pressure of treatment, work intensity, and lacking of rest, which indirectly increased the probability of infection for HCWs; shortage of PPE ; and inadequate training to infection prevention and control for front-line HCWs (except infectious disease physicians).

Guidance on infection prevention and control strategies for use when COVID-19 is suspected has been issued by WHO as early as in March 2020 (https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-(ncov)-infection-is-suspected-20200125). This guidance was intended for HCWs, healthcare managers and IPC teams at the facility level but it was also relevant for the national and district/provincial level. More detailed practical recommendations could also be found at : https://www.who.int/teams/risk-communication/health-sector.

Additional recommendations are available at country level, as done for instance in Canada (Wax Can J Anaesth 2020, see ***below***).

Personal protection of health-care workers

Very early in the epidemic, available epidemiological data showed that not only can subclinical patients transmit the virus effectively but patients can also shed high amounts of the virus and infect others even after recovery from the acute illness. Chang (Lancet Resp Med 2020, see ***below***) concluded that these findings warrant aggressive measures (such as N95 masks, goggles, and protective gowns) to ensure the safety of HCWs during the COVID-19 outbreak especially in the initial stages where limited information about the transmission and infective potency of the virus is available. Wang (J Hosp Inf 2020, see ***below***) presented data supporting the efficacy of N95 respirators, disinfection and hand washing to reduce risk of COVID-19 transmission among medical staff at Zhongnan Hospital of Wuhan University.

A systematic review and meta-analysis of randomized trials by Bartoszko (Influenza Other Respir Viruses 2020, see ***below***) compared medical masks to N95 respirators in preventing laboratory confirmed viral infection and respiratory illness including coronavirus. Compared to N95 respirators; the use of medical masks did not increase laboratory confirmed viral (including coronaviruses) respiratory infection (OR 1.06; 95% CI 0.90-1.25; I2 =0%; low certainty in the evidence) or clinical respiratory illness (OR 1.49; 95%CI 0.98-2.28; I2 =78%; very low certainty in the evidence). Only one trial evaluated coronaviruses separately and found no difference between the two groups (p=0.49).

Of note, a limitation to the effectiveness of face masks was first raised when a medical expert, who visited Wuhan to investigate the COVID-19 outbreak, after returning to Beijing, initially exhibited conjunctivitis of the lower left eyelid before the appearance of catarrhal symptoms and fever. The individual tested positive for COVID-19, suggesting the virus tropism to non-respiratory mucosal surfaces (Chang Lancet Resp Med 2020, see ***below***).

Yan (Dermatol Ther 2020, see ***below***) presented a consensus of Chinese experts on protective measures and advice on hand-cleaning- and medical-glove-related hand protection, mask- and goggles-related face protection, UV-related protection, eye protection, nasal and oral mucosa protection, outer ear and hair protection. The authors noted that insufficient and excessive protection will have adverse effects on the skin and mucous membrane barrier and that using moisturizing products is highly recommended to achieve better protection.

Zhao (J Cardiothorac Vasc Anesth 2020, see ***below***) described more specifically the level 3 personal protective measures for healthcare workers to be used for emergency procedures in patients with confirmed or suspected SARS-CoV-2 infection in China. They included hand disinfection, wearing a cap, a medical protective mask, goggles/face screens/eye protective surgical masks, isolation gowns/protective suits, shoe-covers and gloves.

A review by Cook (Anaesthesia 2020, see ***below***) indicated that personal protective equipment is an important component, but only one part, of a system protecting staff and other patients from COVID-19 cross-infection. Appropriate use significantly reduces risk of viral transmission. Personal protective equipment should logically be matched to the potential mode of viral transmission occurring during patient care - contact, droplet, or airborne. Recommendations from international organisations are broadly consistent, but equipment use is not. Only airborne precautions include a fitted high-filtration mask, and this should be reserved for aerosol-generating procedures.

Uncertainty remains around certain details of personal protective equipment including use of hoods, mask type and the potential for re-use of equipment.

Due to the risk of hand-skin damage, it has also been recommended that HCWs are instructed about rational hand-hygiene measures respectful of the skin along with proper use of protective gloves and moisturizers (Cavanagh J Am Acad Dermatol 2020, see ***below***).

Availability of medical supplies

A comment by Wang (Biosci Trends 2020, see ***below***) addressed the importance of medical supplies availability. As the pandemic developed in China, a serious dearth of emergency medical supplies emerged, and especially an extreme shortage of personal protective equipment such as masks and medical protective clothing. This is considered as one of the major factors affecting the progress of epidemic prevention and control.

Facilities

As of February 19th, the Chinese government converted 13 large-scale public places in Wuhan into makeshift hospitals for patients with COVID-19 with mild symptoms. Chen (J Hosp Inf 2020, see ***below***) noted that insufficient ventilation in these makeshift hospitals may increase infection risk of opportunistic airborne transmission.

Patient flow and triage

In February 2020, an innovative approach was developed in the United Kingdom to stop unnecessary ambulance use and hospital visits, whereby people with suspected COVID-19 are being tested in their homes (Mahase BMJ 2020, see ***below***). The community testing scheme started at the end of January at North West London NHS Trust and has now been implemented in other trusts. More than 130 patients have been reported to be tested in two weeks. Mahase (BMJ 2020, see ***below***) subsequently indicated that in Wales, 90% of suspected cases are managed at home. Members of the public who call NHS or 111 and are assessed as a possible case, are evaluated for their suitability for home testing on the basis of their self-reported health status and their ability to self-isolate at home. Public Health Wales's microbiology team then coordinates with the relevant health board community testing teams to arrange home testing within 12-36 hours.

Safety of procedures

Wong (Can J Anaesth 2020, see ***below***) described the outbreak response measures of the anaesthetic department of 2 hospitals in Singapore. These included engineering controls such as identification and preparation of an isolation operating room, administrative measures such as modification of workflow and processes, introduction of personal protective equipment for staff, and formulation of clinical guidelines for anaesthetic management.

Aerosol-generating procedures, such as non-invasive ventilation (NIV), high-flow nasal cannula (HFNC), bag-mask ventilation, and intubation are of particularly high risk when dealing with COVID-19 patients. Cheung (Lancet Respir Med 2020, see ***below***) described the approach developed by a local intensive care unit in a Hong Kong hospital to managing the risks to health-care staff, while maintaining optimal and high-quality care. They did not recommend using NIV or HFNC until the patient is cleared of COVID-19. Airway devices providing 6 L/min or more of oxygen were considered high-flow and they discouraged their use if an airborne infection isolation room is unavailable. They recommended that endotracheal intubation is done by an expert specialised in the procedure, and early intubation considered in a patient with deteriorating respiratory condition. They recommended avoiding bag mask ventilation for as long as possible; and optimising preoxygenation with non-aerosol-generating means. Methods included the bed-up-head-elevated position, airway manoeuvres, use of a positive end expiratory pressure valve, and airway adjuncts.

Zuo (Chin Med Sci J. 2020, see ***below***) noted that endotracheal intubation may put the anaesthesiologists at high risk of nosocomial infection. In fact, SARS-CoV-2 infection of anaesthesiologists after endotracheal intubation for confirmed COVID-19 patients have been reported in hospitals in Wuhan. The expert panel of airway management in

Chinese Society of Anaesthesiology drafted a recommendation to guide the performance of endotracheal intubation by frontline anaesthesiologists and critical care physicians.

Zhang (Anesthesiology 2020, see ***below***) also reported that the Wuhan Union Hospital's Department of Anaesthesiology drafted the "Perioperative Care Provider's Considerations in Managing Patients with COVID-19" and carried out 45 surgical procedures on such patients. An upgraded surgical safety checklist for patients with suspected or confirmed COVID-19 was drawn up and implemented, along with infection-control guidelines for the care of such patients. Task forces dedicated to procedure standardization, infection control, and staff scheduling within anaesthesia were quickly assembled in most hospitals across the country. Monitoring was implemented to ensure that anaesthesia providers wore and removed personal protective equipment before working in the perioperative environment. Drills were held to ensure the optimal management of emergencies, with mandatory multidisciplinary participation across anaesthesia, surgery, critical care, paediatrics, and obstetrics and gynaecology.

Of note, another report noted that during pandemics the number of intensive care unit beds for mechanical ventilation through tracheal intubation could rapidly become insufficient. Therefore, non-invasive ventilation could be required outside the intensive care unit. To increase safety during NIV, use of a helmet has been suggested by Cabrini (Lancet 2020, see ***below***).

In order to limit the risk of nosocomial transmission, Chen, Tian et al. (Lancet Inf Dis 2020, see ***below***) reported the use of an innovative infection-control system in a Guangdong hospital, called the "observing system", whereby cameras cover the negative pressure isolation ward and infection control observers monitor medical staff and provide assistance in real time via computer monitors. The main responsibilities of these infection control observers are to maintain the normal operation of the negative pressure isolation wards, supervise the implementation of disinfection, ensure a sufficient supply of protective materials, arrange specimens for inspection, and relieve anxiety of the medical personnel while treating patients.

A role for telehealth and telemedicine

The COVID-19 pandemic has had unprecedented global effects, yet the rapid emergence of telehealth across the globe has allowed healthcare professionals to connect virtually with patients and families while following safe social distancing guidelines (reviewed by Cohen Curr Opin Cardiol 2020, see ***below***). For instance, Zhai (manuscript on MedRXiv : https://www.medrxiv.org/content/10.1101/2020.02.20.20025957v1) described the Emergency Telemedicine Consultation System (ETCS), a telemedicine-enabled outbreak alert and response network, established by the National Telemedicine Center of China in Zhengzhou. ETCS was built upon a doctor-to-doctor (D2D) approach, in which health services can be accessed remotely through terminals across hospitals. The system architecture of ETCS comprises three major architectural layers: (1) telemedicine service platform layer, (2) telemedicine cloud layer, and (3) telemedicine service application layer. The ETCS has demonstrated substantial benefits in terms of the effectiveness of consultations and remote patient monitoring, multidisciplinary care, and prevention education and training.

Hollander (NEJM 2020, see ***below***) presented the benefits that can be expected from telemedicine. Direct-to-consumer (or on-demand) telemedicine allows patients to be efficiently screened. It is both patient-centered and conducive to self-quarantine, and it protects patients, clinicians, and the community from exposure. It can allow physicians and patients to communicate 24/7, using smartphones or webcam-enabled computers. Health care providers can easily obtain detailed travel and exposure histories. Automated screening algorithms can be built into the intake process, and local epidemiologic information can be used to standardize screening and practice patterns across providers. Interestingly, more than 50 U.S. health systems already have such programs, and systems lacking such programs can outsource similar services. However, the authors also identified the numerous challenges to be faced (incl. reimbursement) before such approach can be used in the management of COVID-19 in the U.S.

Greenhalgh (BMJ 2020, see ***below***) reported that video could be useful for people with heightened anxiety (for whom a video consultation may be more reassuring than a phone call), those with mild symptoms suggestive of coronavirus (for which visual cues may be useful), and those with more severe symptoms (when a video consultation may reduce the need to visit a potentially contagious patient). Well patients seeking general advice could be directed to a website or recorded phone message. Moreover, there may be a trade-off between staying at home and coming to clinic for a full examination—for example, in frail older patients or immunosuppressed patients.

A study by Khairat (JMIR Public Health Surveill 2020, see ***below***) assessed the potential of a system call Virtual Care. The study included 733 total virtual visits, including 257 (35%) with COVID-19-like symptoms. Of the COVID-19 like visits, the number of females was 178 (70%). People in the 30-39 years of age (26%) and 40-49 years (25%) were 50% of the total patients. Virtual Care was shown to provide efficient triaging. The authors concluded that Virtual Care is capable to reduce emergency room visits, conserve healthcare resources, and avoid the spread of COVID-19 by treating patient remotely.

It is well recognized that telehealth visits will not supplant all patient-physician interactions, but is a very acceptable first step in the majority of cases and can often steer the patient to subsequently undergo more selective and streamlined care.

Screening approaches

It has been reported that Thailand had 58 international flights connecting with Wuhan (Sriwijitalai Int J Prev Med 2020, see ***below***). At the start of the epidemic, active screening at the airport (by body temperature scanning and clinical history taking) has been done to identify possible infected cases. In the first month, active screening identified 12 cases with positive result. However, the final diagnosis by molecular diagnostic tests could identify only one case with SARS-CoV-2 infection, which was the first case report of infection outside China. The other 11 cases were infected with influenza virus.

As reported by Ge (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.02.20.20025973v1), symptom-based mass screening and testing intervention (MSTI) can identify a large fraction of infected individuals during an infectious disease outbreak. China is currently using this strategy for the COVID-19 outbreak. The authors noted that this might lead to increased transmission if not properly implemented. The outcome of a modelling study suggested that the approach can be useful if the probability of transmission at testing sites is less than the probability that a symptomatic person is infected with SARS-CoV-2. This type of data is important to generate, as it may support recommendations such as for instance the use of dedicated testing sites separate from the usual healthcare facilities.

Gostic (Elife 2020, see ***below***) estimated the impact of different screening programs given current knowledge of key COVID-19 life history and epidemiological parameters. Even under best-case assumptions, the authors predicted that screening will miss more than half of infected people. Most cases missed by screening are fundamentally undetectable, because they have not yet developed symptoms and are unaware that they were exposed.

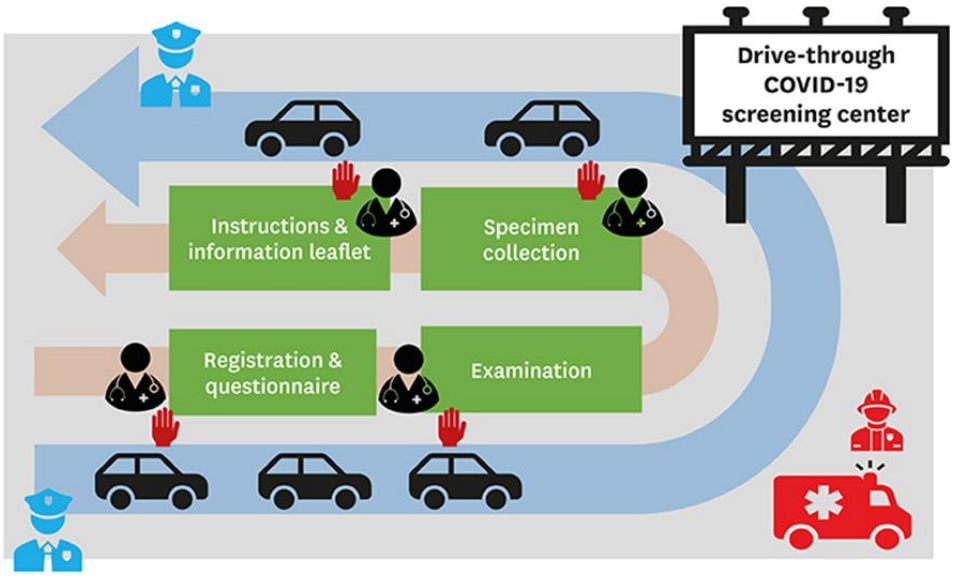
Rao (Infect Control Hosp Epidemiol 2020, see ***below***) proposed to use machine learning algorithms to help improve possible COVID-19 case identifications using a mobile phone-based web survey capturing with the most common manifestations of disease, along with basic travel history.

For safe and efficient screening for COVID-19, drive-through screening centres have been designed and implemented in South Korea. Kwon (J Korean Med Sci 2020, see ***below***) presented the overall concept, advantages, and limitations of these screening centres. The steps of the drive-through centres include registration, examination, specimen collection, and instructions (***Figure 22***). The entire service takes about 10 minutes for one testee without leaving his or her car. Increased testing capacity over 100 tests per day and prevention of cross-infection between testees in the

waiting space were reported as major advantages, while protection of staff from the outdoor atmosphere was said to be challenging.

Choi (Clin Exp Emerg Med 2020, see ***below***) compared the advantages and disadvantages of Drive-Through and Walk-Through methods of testing. Similar drive-through testing centers have been reported in Israel for instance (Kim Disaster Med Public Health Prep 2020, see ***below***).

Figure 22 Illustration of drive-through COVID-19 screening centre provided for the public in South Korea (from Kwon J Korean Med Sci 2020)



Contact tracing

When several unknown epidemiological and clinical characteristics of the disease remain and an effective medical intervention is lacking (as in the case of COVID-19), contact management becomes one of the core strategies to minimize additional transmission. A WHO interim guideline of May 2020 provides guidance on how to establish contact tracing capacity for the control of COVID-19 (https://www.who.int/publications/i/item/contact-tracing-in-the-context-of-covid-19). Another WHO document also offers operational guidance to Member States for the rapid investigation of suspected COVID-19 cases (https://www.who.int/publications-detail/considerations-in-the-investigation-of-cases-and-clusters-of-covid-19). This guidance may be implemented in different countries with varying resources and epidemiological patterns and it is expected to be adapted accordingly.

A contact is defined as a person who has experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:
1. face-to-face contact with a probable or confirmed case within 1 metre and for at least 15 minutes
2. direct physical contact with a probable or confirmed case
3. direct care for a patient with probable or confirmed COVID-19 disease without using recommended personal protective equipment
OR
4. other situations as indicated by local risk assessments.

Among the first 10 patients with travel-related confirmed COVID-19 reported in the United States, a total of 445 persons (range = 1-201 persons per case) who had close contact with one of the 10 patients on or after the date of the patient's symptom onset were identified (Burke MMWR Morb Mortal Wkly Rep 2020, see ***below***). 222 (50%) were health care personnel. Active symptom monitoring of the 445 close contacts, consisting of daily telephone, text, or in-person inquiries about fever or other symptoms for 14 days following the last known exposure to a person with confirmed COVID-19, was conducted by local health jurisdictions.

Contact tracing is typically triggered by a confirmed index case identified via symptom-based surveillance (Endo, manuscript on medRxiv, see https://www.medrxiv.org/content/10.1101/2020.08.01.20166595v1). Traditional investigative methods, depending on the patient or proxy interview, has the limitation of omissions and errors associated with recalling previous activities (COVID-19 National Emergency Response Center Osong Public Health Res Perspect 2020, see ***below***). In South Korea for instance, the methods used to overcome recall and confirmation biases that can occur while determining the location of the contact include checking medical facilities records, phone-based global positioning system (GPS), card transaction records, and closed-circuit television (CCTV).

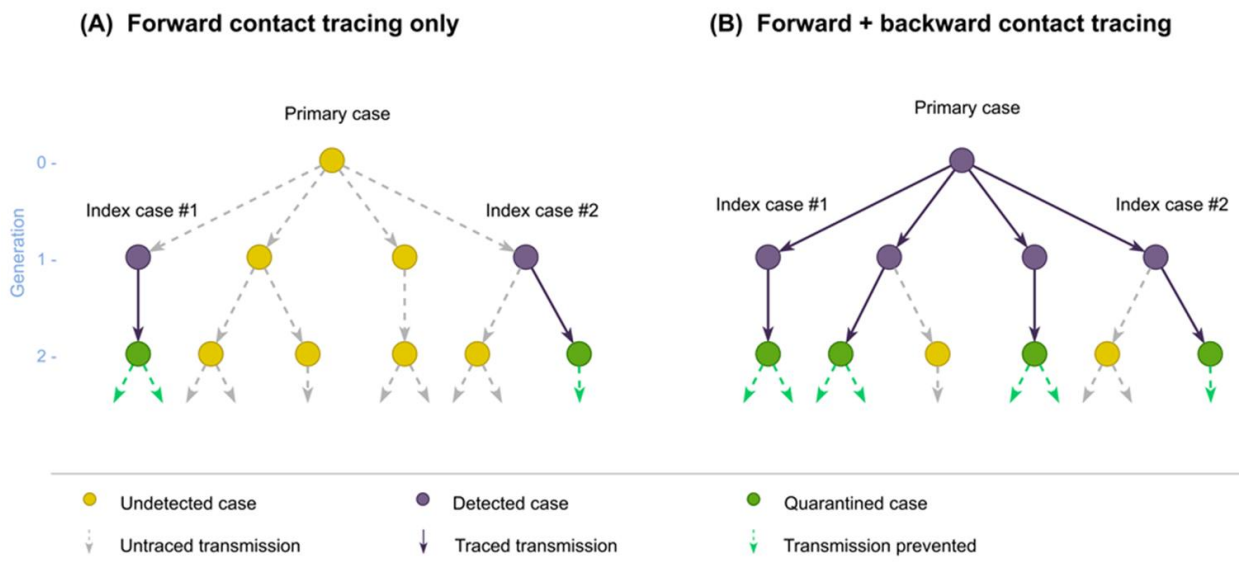
Pan (Irish J Med Sci 2020, see ***below***) also reported that several personal-oriented and mobile phone-based information technologies were developed and widely used in China. For instance, the application "Diagnosed Cases in Community" enables people to check the distribution of COVID-19 cases in local communities on the map. The map covers more than 130 cities in China and shows case number and location.

Kamel Boulos (Int J Health Geogr 2020, see ***below***) described a range of online/mobile geographic information systems (GIS) and applications for tracking the coronavirus epidemic and associated events as they unfold around the world. Some of these dashboards and applications are receiving data updates in near-real-time (at the time of writing).

However, as noted by Buckee (Science 2020, see ***below***), the protection of personal privacy must be paramount. Consent-based data sharing models and data protection laws provide for the legal grounds to use personal data during emergencies. However, the use of individual data is not advocated by all experts.

Contacts of this index case are thus identified via interviews by public health officials (manual contact tracing) or by tracking proximity records on digital devices (digital contact tracing), and then asked to quarantine in order to prevent further transmissions (Endo, manuscript on medRxiv, see https://www.medrxiv.org/content/10.1101/2020.08.01.20166595v1).

Figure 23. Schematic illustration of forward and backward contact tracing (from Endo 2020)



Contact tracing often targets 'downstream' individuals, who may have been infected by the index case ('forward tracing'); i.e. those who have been in contact with the index case after the index case likely became infectious (often assumed as 2 days before illness onset for COVID-19). However, 'backward tracing' can also be used to identify the upstream primary case who infected the index case (or a setting or event at which the index case was infected) by retracing history of contact to the likely point of exposure, i.e. up to 14 days prior to symptom onset (***Figure 23***). If this primary case is identified, a larger fraction of the transmission chain can be detected by forward tracing each of the

contacts of this primary case. This approach is particularly valuable when there is high individual-level variation in the number of secondary transmissions. By using a simple branching process model, Endo explored the potential of combining backward contact tracing with more conventional forward contact tracing for control of COVID-19.

Immunity passports

A widely discussed idea in the media has been the issuance of "immune passports," the proposed use of serology to infer immunity and thus enable a person to work on the front lines or return to daily work routines when containment measures are in place (Bryant Sci Imm 2020, see ***below***). Such an application must be predicated on an established surrogate of protection, a given antibody end point associated with clinical protection from infection, and a test with sufficient specificity to ensure people are not unintentionally put in harm's way. On April 24, WHO indicated that there was no evidence that people who have recovered from COVID-19 and have antibodies are protected from a second infection (https://www.who.int/publications/i/item/10665-331866). A most recent review on this topic is provided by Brown (Lancet Infect Dis 2020, see ***below***).

Face masks

Liu (Influenza Other Respir Vir 2020, see ***below***) reported an interesting anecdote suggesting the efficacy of face masks to present transmission of SARS-CoV-2. The authors observed a typical case of cluster outbreak caused by public transportation exposure during the outbreak of COVID-19. One patient from Chongqing, China, didn't wear a face mask in the first vehicle, while he wore a face mask in the second vehicle he took. This male patient with COVID-19 found himself coughing. Unaware of the fact that he might have been infected with COVID-19 and in a hurry, he didn't manage to get a face mask before he took the coach bus from the city back to his county. Many passengers didn't wear face masks on the same coach bus. The duration of this bus was 2 hours and 10 minutes; there were 39 other passengers on the same coach bus. According to epidemiological survey, 5 other passengers on the same coach bus were infected. Upon arrival in the county, this male patient bought a face mask and took a minibus to his final destination wearing the mask. The duration of minibus was 50 minutes, there were 14 other passengers on the same minibus. The Centre for Disease Control and Prevention conducted an epidemiological investigation and close contact tracing management. The passengers on the minibus that were screened and treated as suspected cases. A 14-day medical observation period was conducted. During the observation period, passengers were taken temperature twice a day. All the passengers did not have fever, cough or other abnormal symptoms, two quantitative RT-PCR test results were negative. No passengers were infected in the same minibus.

In the first weeks of the pandemic, the sudden surge of demand on facemasks in East Asia (together with reduced productivity in China and other factors) contributed to a global shortage that in turn disrupted supplies to health care providers worldwide. This unprecedented global shortage of medical facemasks was accompanied by contrasting views on the utility of medical facemasks among the public but also governments and public health experts.

Efficacy of face masks

An overview by Chan published on March 31st indicated that for infected individuals, facemasks are likely to be superior to active practices such as covering up the nose or mouth when sneezing or coughing (Int J Epidemiol 2020, see ***below***). However, a small study in 4 patients by Bae (Ann Intern Med 2020, see ***below***) concluded that both surgical and cotton masks seem to be ineffective in preventing the dissemination of SARS-CoV-2 from the coughs of patients with COVID-19 to the environment and external mask surface.

A meta-analysis by Chu (Lancet 2020, see ***below***) assessed the use of face masks and eye protection to prevent transmission of viruses in a more systematic way. The study found that face mask use could result in a large reduction in risk of infection (n=2647; aOR 0·15, 95% CI 0·07 to 0·34, RD −14·3%, −15·9 to −10·7; low certainty), with stronger associations with N95 or similar respirators compared with disposable surgical masks or similar (e.g., reusable 12–16-

layer cotton masks; pinteraction=0·090; posterior probability >95%, low certainty). Eye protection also was associated with less infection (n=3713; aOR 0·22, 95% CI 0·12 to 0·39, RD −10·6%, 95% CI −12·5 to −7·7; low certainty).

Mandates for mask use in public during the recent COVID-19 pandemic, worsened by global shortage of commercial supplies, have led to widespread use of homemade masks and mask alternatives. It is assumed that wearing such masks reduces the likelihood for an infected person to spread the disease, but many of these mask designs have not been tested in practice. Fischer (Sci Advances 2020, see ***below***) presented a simple optical measurement method to evaluate the efficacy of masks to reduce the transmission of respiratory droplets during regular speech. In proof-of-principle studies, the authors compared a variety of commonly available mask types and observed that some mask types approach the performance of standard surgical masks, while some mask alternatives, such as neck fleece or bandanas, offer very little protection. A review by Jain (Cureus 2020, see ***below***) indicated that household fabrics such as cotton T-shirts and towels have some filtration efficacy and therefore potential for droplet retention and protection against virus-containing particles. However, the percentage of penetration in cloth masks was found higher than surgical masks or N95 respirators. The authors concluded that cloth masks have limited inward protection in healthcare settings where viral exposure is high, but may be beneficial for outward protection in low-risk settings and use by the general public where no other alternatives to medical masks are available.

Solving shortage and environmental issues

As noted by Das (Sci Total Envir 2020, see ***below***), billions of facemasks are produced from petrochemicals derived raw materials, which are non-degradable upon disposal after their single use, thus causing environmental pollution and damage. The sustainable way forward is to utilise raw materials that are side-stream products of local industries to develop facemasks having equal or better efficiency than the conventional ones.

Swennen (Int J Oral Maxillofac Surg 2020, see ***below***) presented a proof of concept and prototype demonstrating a reusable custom-made three-dimensionally (3D) printed face mask based on materials and techniques (3D imaging and 3D printing) with global availability. The individualized 3D protective face mask consists of two 3D-printed reusable polyamide composite components (a face mask and a filter membrane support) and two disposable components (a head fixation band and a filter membrane).

Das indicated that wheat gluten biopolymer, a by-product or co-product of cereal industries, can be electrospun into nanofibre membranes and subsequently carbonised at over 700 °C to form a network structure, which can simultaneously act as the filter media and reinforcement for gluten-based masks (Sci Total Envir 2020, see ***below***). In parallel, the same gluten material can be processed into cohesive thin films using plasticiser and hot press. Additionally, lanosol, a naturally-occurring substance, imparts microbe resistance in gluten plastics. Thus, thin films of flexible gluten with very low amounts of lanosol can be bonded together with the carbonised mat and shaped by thermoforming to create the facemasks. The carbon mat acting as the filter can be attached to the masks through adapters that can also be made from injection moulded gluten.

Among other proposed strategies for mitigating the massive demand for N95 FFRs is their reuse after a process of decontamination that allows the inactivation of any potentially infectious material on their surfaces. A review by Rodriguez-Martinez (Am J Infect Control 2020, see ***below***) summarized available evidence on the different inactivation methods available. In July 2020, a review by Steinberg (Can J Anaesth 2020, see ***below***) found that moist mask heating (65-80°C at 50-85% relative humidity for 20-30 min) and vaporous hydrogen peroxide treatment were supported by the literature to provide consistent viral decontamination without compromising mask seal and filtration efficiency. Other investigated decontamination methods lacked comprehensive scientific evidence for all three of these key criteria.

Efficacy of non-pharmaceutical interventions

A manuscript by Tian (Science 2020, see ***below***) provided a preliminary evaluation of the efficacy of control measures implemented in China. The Wuhan city travel ban is considered to have slowed the dispersal of infection to other cities by an estimated 2.91 days (95% CI, 2.54-3.29) on average. Among the other urban centres across mainland China, cities that implemented control measures pre-emptively, before the first case was reported, had 37% fewer cases in the week following the first reported case (13.0, 95%CI 7.1-18.8) compared with cities starting control after the first case (20.6, 95%CI 14.5-26.8). Among individual control measures investigated, the most effective were suspending intra-city public transport, and closing entertainment venues and banning public gatherings.

Chu (Lancet 2020, see ***below***) conducted a systematic review and meta-analysis to investigate the optimum distance for avoiding person-to-person virus transmission. The authors identified 172 observational studies across 16 countries and six continents, with no randomised controlled trials and 44 relevant comparative studies in health-care and non-health-care settings (n=25 697 patients). Transmission of viruses was lower with physical distancing of 1 m or more, compared with a distance of less than 1 m (n=10 736, pooled adjusted odds ratio [aOR] 0·18, 95% CI 0·09 to 0·38; risk difference [RD] −10·2%, 95% CI −11·5 to −7·5; moderate certainty); protection was increased as distance was lengthened (change in relative risk [RR] 2·02 per m; pinteraction=0·041; moderate certainty).

A Cochrane rapid review assessed the effects of quarantine (alone or in combination with other measures) of individuals who had contact with confirmed cases of COVID-19, who travelled from countries with a declared outbreak, or who live in regions with high transmission of the disease (Nussbaumer-Streit Cochrane Database Syst Rev 2020, see ***below***). Evidence for COVID-19 was found limited to modelling studies that make parameter assumptions based on the current, fragmented knowledge of the disease (see ***Modelling the impact of public health measures*** below). Nevertheless, findings consistently indicated that quarantine is important in reducing incidence and mortality during the COVID-19 pandemic.

Bo (Int J Inf Dis 2020, see ***below***) evaluated the effectiveness of four types of non-pharmaceutical interventions in containing the time-varying effective reproduction number (Rt) of COVID-19. The study included 1 908 197 confirmed COVID-19 cases from 190 countries between 23 January and 13 April 2020. Interventions were categorized into four types: mandatory face mask in public, isolation or quarantine, social distancing and traffic restriction. The implementations of mandatory mask, quarantine, distancing and traffic were associated with changes (95%confidence interval, CI) of -15.14% (-21.79% to -7.93%), -11.40% (-13.66% to -9.07%), -42.94% (-44.24% to -41.60%) and -9.26% (-11.46% to -7.01%) in the Rt of COVID-19 compared with those without the implementation of the corresponding measures. Distancing and the simultaneous implementation of two or more types of non-pharmaceutical interventions seemed to be associated with a greater decrease in the Rt of COVID-19. Overall, this study indicated that non-pharmaceutical interventions can significantly contain the COVID-19 pandemic. The authors concluded that distancing and the simultaneous implementation of two or more non-pharmaceutical interventions should be the strategic priorities for containing COVID-19.

Acceptability of public health measures

As outlined by Bero (Am J Public Health 2020, see ***below***), public health measures such as isolation, quarantine, and social distancing have fundamentally changed the way we live.

In Japan, Machida (Int J Infect Dis 2020, see ***below***) evaluated the level of adoption of personal protective measures by citizens. The prevalence of the five personal protective measures (hand hygiene, social distancing measures, avoiding touching the eyes, nose and mouth, respiratory etiquette, and self-isolation) ranged from 59.8% to 83.8%, with the lowest being avoiding touching the eyes, nose, and mouth. In total, 34.7% implemented all personal protective measures. The median daily hand hygiene events were 5 per day (25th percentile, 75th percentile: 3,8). The authors concluded in an insufficient implementation of the protective measure.

A survey of 72,417 adults in 27 countries (Australia, Brazil, Canada, Denmark, Finland, France, Germany, Hong Kong, Italy, Japan, Malaysia, South Korea, Mexico, Netherlands, Norway, Philippines, Saudi Arabia, Singapore, South Korea, Spain, Sweden, Taiwan, Thailand, United Arab Emirates, UK, USA and Vietnam) asked respondents if they would isolate themselves for 7 days if they felt unwell and had certain symptoms of COVID-19 or if they would do so if urged to by a healthcare or public health professional (Daoust PLoS One 2020, see ***below***). It also asked how often they had taken infection-prevention measures such as handwashing, avoiding public transportation, and cleaning often-touched surfaces. Elderly people's response was found substantially similar to their fellow citizens in their 50's and 60's. This research provided the first thorough description of the most vulnerable population's attitudes and compliance in a comparative perspective. It suggested that governments' strategies toward elderly people are far from successful.

Barriers to implementation of interventions

While non-pharmaceutical interventions including physical distancing, isolation, and mask use may flatten the peak in communities (see ***Efficacy of non-pharmaceutical interventions*** above, these strategies rely on community understanding and motivation to engage to ensure appropriate compliance and impact. Seale (BMC Inf Dis 2020, see ***below***) reviewed the key determinants impacting on engagement. The results revealed that there are a range of demographic, social and psychological factors underpinning engagement with quarantine, school closures, and personal protective behaviours. Aside from the factors impacting on acceptance and compliance, there are several key community concerns about their use that need to be addressed including the potential for economic consequences. The authors indicated that understanding the barriers helps identify what strategies need to be adopted to motivate individuals and improve community compliance.

Communication

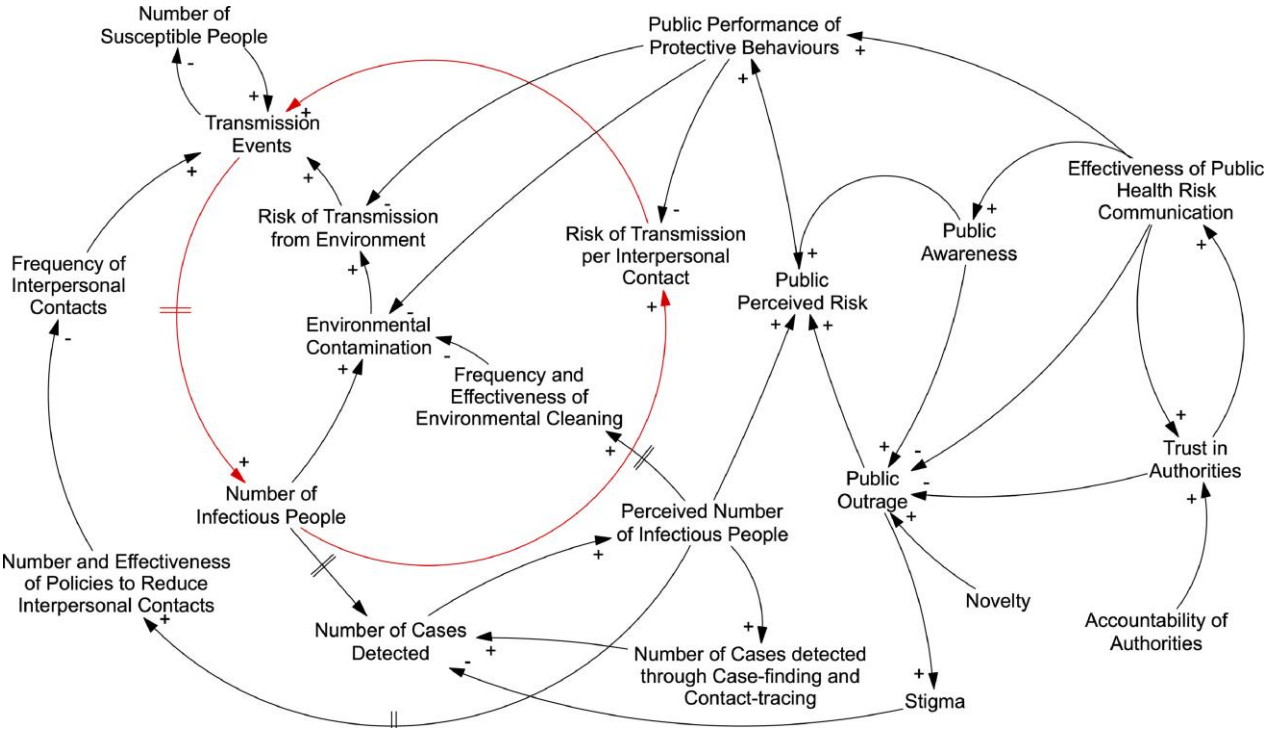
Risk communication, as defined by the World Health Organization, is "the exchange of real-time information, advice and opinions between experts and people facing threats to their health, economic or social well-being." One of the most important and effective interventions in a public health response to any event is to proactively communicate what is known, what is unknown, and what is being done to get more information, with the objectives of saving lives and minimizing adverse consequences (https://www.who.int/risk-communication/background/en/). It is increasingly recognized that society, communities, and patients view risk from a social constructionist approach whereby risk is seen to be interrelated with sociocultural context (Smith Soc Sci Med 2006, see ***below***). This is especially the case during pandemics that have high rates of infection, significant morbidity, lack of therapeutic measures, and rapid increases in cases, all of which - so-called dread factors - apply to the COVID-19 pandemic (Abrams J Allergy Clin Immunol Pract 2020, see ***below***). These factors can be drivers of serious, and often unmeasurable, consequences resulting from heightened risk perception. The scale of the crisis and governments' responses have been matched by a colossal flow of information about COVID-19 in terms of 24/7 news coverage, televised press conferences provided by both political leaders and health authorities, prime time speeches to the people by kings, presidents, prime ministers and religious leaders, as well as news analyses, debates and social media posts (Finset Patient Educ Counsel 2020, see ***below***). Understanding the audiences (class, age, risk, communication style) and tailoring the message to reach the public is thus key to avoid hoarding behaviour (e.g. stockpiling masks, PPEs, curative drugs, toilet paper), anger and outrage (e.g. demonstration against masks wearing regulations, lockdown enforcement), mistrust (e.g. multiple experts and shifting inconsistent messages), panic or paranoia and fear (e.g. hospital avoidance, stigmatisation of nationals of some countries, denunciation of people perceived as sick or not complying with the COVID-19 measures). The alteration of the number of people allowed to meet over the course of the crisis - the social bubble - is an example of poor risk-benefit communication by the Belgian authorities. On several occasions, the bubble expanded or contracted and the mere principle of who can be part of your bubble of 15, 10 or 5 people was poorly understood by citizens, as evidenced by interviews in trusted television and radio channels. The same confusion and misunderstanding were observed in relation to face mask use messages. Shifting from an initial message that masks were not needed to an obligation of wearing masks lead to mistrust and reduced confidence in political and health

experts alike. This forced the government to resort to strict *manu militari* law enforcement under the new "paradigm" - masks are now saving lives. The misbehaviour and non-compliance to the new rules and the strong response (i.e. fines and imprisonment sentence threat) triggered outrage and even more mistrust in official channels. Such inconsistent message, shifting on a short time scale from one measure to its complete contrary by the same political and health experts have affected individuals at different degrees with potentially serious psychological long-term effect. Mental health is as important to protect as physical health during a health crisis, especially if the cause is invisible, unknown, novel, deadly and reported in a sensationalistic manner. Hope can heal fear as exemplified by the shortage of hydroxychloroquine as far as the small rural clinic in Eastern African countries - that had then not yet been hit by the virus – only a few days after the statement about its curative properties on COVID-19 was released.

Systems approaches

Bradley (EClinicalMedicine 2020, see ***below***) highlighted the importance of a systems approach to help policymakers understand and influence the spread of infection and its multifaceted consequences across the community. The author outlined a causal loop diagram to illustrate some important interacting components in a society that is responding to the threat of COVID-19 (***Figure 24***).

Figure 24 An example causal loop diagram illustrating some of the interacting components in a society responding to the threat of COVID-19 (from Bradley EClinicalMedicine 2020)



Modelling studies

An impressive number of modelling studies related to COVID-19 has been reported since the beginning of the epidemic. In March 2020, Roy Anderson (Lancet 2020, see ***below***) provided an interesting discussing on the various unknowns that remained with regard to the epidemiology of the disease and the expected impact of various public health strategies. The aim of modelling studies was indeed not only to characterize the epidemiology of the disease in various countries, but also to predict the impact of the public health measures that could be implemented. Numerous publications (with date of issue up to April 1st) can be found at https://github.com/midas-network/COVID-19/wiki/Documents#estimate. The examples presented in the 2 sections below are classified according to the objectives of the study.

Of note, Roda (Inf Dis Modelling 2020, see ***below***) demonstrated that non-identifiability in model calibrations using the confirmed-case data is the main reason for the wide variations observed across prediction models for the COVID-19 epidemics in Wuhan and other parts of China. The authors suggested that predictions using more complex models may not be more reliable compared to using a simpler model.

Jewell (JAMA 2020, see ***below***) addressed the topic of epidemic modelling and accuracy of projections. It indicated for instance, that for large countries, such as the USA, modelling is more problematic because of heterogeneous subepidemics in local areas. Individual characteristics, such as age and comorbidities, influence the risk of serious disease from COVID-19, but population distributions of these factors vary widely in the USA.

Modelling key characteristics of the epidemic

- Pan (on medRxiv https://www.medrxiv.org/content/10.1101/2020.02.19.20025387v3) described 2 mathematical models simulating the epidemic in Wuhan and other parts of China, taking into account the mobility of people. The data suggest that the peak of new asymptomatic cases per day in Wuhan occurred on February 6, and the peak of new symptomatic infections on February 3. The model predicts that COVID-19 cases will gradually wane by the end of April 2020, both in Wuhan and the other parts of China.
- Based on the 199 first confirmed cases on the Diamond Princess cruise ship, Nishiura (J Clin Med 2020, see ***below***) employed a back-calculation method to estimate the incidence of infection. Without the movement restriction policy imposed from 5 February, it was predicted that the cumulative incidence with and without close contact would have been as large as 1373 (95% CI: 570, 2176) and 766 (95% CI: 587, 946) cases, respectively, out of a total of 3711 persons (2666 passengers and 1045 crew members). With the application of a Bayesian model to data from the same outbreak, the R0 was estimated as high as 5.71 (95% credible interval: 4.08-7.55) (Chao-Chih, manuscript on medRxiv: https://doi.org/10.1101/2020.06.21.20136465). The simulated trajectory showed the entire epidemic period without containment measurements was approximately 47 days and reached the peak one month after the index case.
- Thompson (J Clin Med 2020, see ***below***) estimated the probability that an imported case is followed by sustained human-to-human transmission to 0.41 (credible interval [0.27, 0.55]).
- Tuite (Lancet Inf Dis 2020, see ***below***) suggested that the numerous COVID-19 case exportations from Italy early March indicated an epidemic that was larger than official case counts suggested. The authors estimated non-identification of cases to reach 72% (61–79%) of cases, corresponding to a true outbreak size of 3971 cases (95% CI 2907–5297) vs. a reported case count of 1128 on Feb 29, 2020.
- De Salazar (Em Inf Dis 2020, see ***below***) used air travel volume estimates from Wuhan, China, to international destinations and a generalized linear regression model to identify locations that could have undetected imported cases. The data led to a recommendation of rapid strengthening of surveillance and control efforts in locations like Indonesia. By contrast, India and Singapore were found to have more cases reported than expected from the model.
- Li (Science 2020, see ***below***) used observations of reported infections within China, in conjunction with mobility data, a networked dynamic metapopulation model and Bayesian inference, to infer critical epidemiological characteristics associated with SARS-CoV2, including the fraction of undocumented infections and their contagiousness. The authors estimated 86% of all infections were undocumented (95% CI: 82%–90%) prior to 23 January 2020 travel restrictions. Per person, the transmission rate of undocumented infections was 55% of documented infections (46%–62%), yet, due to their greater numbers, undocumented infections were the infection source for 79% of documented cases. These findings help explain the rapid geographic spread of SARS-CoV-2 and indicate containment of this virus is particularly challenging.
- Rocklöv (J Travel Med 2020, see ***below***) noted that empirical observations suggesting population density can have large impacts on R0 through the contact rates. On the Diamond Princess cruise ship, both the population

density and R0 was estimated approximately four times greater than that in Wuhan. Therefore, the authors recommend avoiding situations with higher population densities to limit the spread of COVID-19.

- Kissler (Science 2020, see ***below***) used estimates of βCoVs OC43 and HKU1 to inform a model of SARS-CoV-2 transmission. The authors projected that recurrent wintertime outbreaks of SARS-CoV-2 will probably occur after the initial, most severe pandemic wave. They suggested that, to avoid exceeding critical care capacities, prolonged or intermittent social distancing may be necessary into 2022. Moreover, they predicted that even in the event of apparent elimination, a resurgence in contagion could be possible as late as 2024.
- Debora MacKenzie (New Scientist 2020, see ***below***) referred to modelling data suggesting that only 10 per cent of cases are responsible for 80 per cent of transmission.
- Kim (Epidemiol Health 2020, see ***below***) modelled the COVID-19 outbreak in the Republic of Korea by applying a mathematical model of transmission that factors in behavioural changes. The model demonstrated that the relatively high per-capita rate of transmission and the low rate of changes in behaviour have caused a large-scale transmission of COVID-19 in the Daegu/Gyeongbuk area in the Republic of Korea.
- Age disparities in observed cases could be explained by children having lower susceptibility to infection, lower propensity to show clinical symptoms or both. Davies (Nat Med 2020, see ***below***) evaluated these possibilities by fitting an age-structured mathematical model to epidemic data from China, Italy, Japan, Singapore, Canada and South Korea. The authors estimated that susceptibility to infection in individuals under 20 years of age is approximately half that of adults aged over 20 years, and that clinical symptoms manifest in 21% (95% credible interval: 12-31%) of infections in 10- to 19-year-olds, rising to 69% (57-82%) of infections in people aged over 70 years.

Modelling the impact of public health measures

- Gostic estimated the effectiveness of symptom and risk screening to prevent the spread of COVID-19 (Elife. 2020, see ***below***)
- Anzai assessed the impact of reduced travel on exportation dynamics of COVID-19 (J Clin Med 2020, see ***below***)
- Hellewell (Lancet Glob Health 2020, see ***below***) used a mathematical model to assess if isolation and contact tracing are able to control onwards transmission from imported cases of COVID-19. The authors found that the probability of controlling an outbreak decreased with the number of initial cases, when R0 was 2·5 or 3·5 and with more transmission before symptom onset. Across different initial numbers of cases, the majority of scenarios with an R0 of 1·5 were controllable with less than 50% of contacts successfully traced. To control the majority of outbreaks, for R0 of 2·5 more than 70% of contacts had to be traced, and for an R0 of 3·5 more than 90% of contacts had to be traced. The delay between symptom onset and isolation had the largest role in determining whether an outbreak was controllable when R0 was 1·5. For R0 values of 2·5 or 3·5, if there were 40 initial cases, contact tracing and isolation were only potentially feasible when less than 1% of transmission occurred before symptom onset.
- Chinazzi (Science 2020, see ***below***) used a global metapopulation disease transmission model to project the impact of travel limitations on the national and international spread of the epidemic. The model was calibrated based on internationally reported cases, and shows that at the start of the travel ban from Wuhan on 23 January 2020, most Chinese cities had already received many infected travellers. The travel quarantine of Wuhan delayed the overall epidemic progression by only 3 to 5 days in Mainland China, but had a more marked effect at the international scale, where case importations were reduced by nearly 80% until mid-February. Modelling results also suggested that sustained 90% travel restrictions to and from Mainland China only modestly affected the epidemic trajectory unless combined with a 50% or higher reduction of transmission in the community.

- Wells (PNAS 2020, see ***below***) estimated the impact of these control measures and investigated the role of the airport travel network on the global spread of the COVID-19 outbreak. Our results show that the daily risk of exporting at least a single SARS CoV-2 case from mainland China via international travel exceeded 95% on January 13, 2020. The authors found that 779 cases (95% CI: 632 to 967) would have been exported by February 15, 2020 without any border or travel restrictions and that the travel lockdowns enforced by the Chinese government averted 70.5% (95% CI: 68.8 to 72.0%) of these cases. In addition, during the first three and a half weeks of implementation, the travel restrictions decreased the daily rate of exportation by 81.3% (95% CI: 80.5 to 82.1%), on average.
- Lau (J Trav Med 2020, see ***below***) evaluated whether rigorous lockdown measures as implemented by China have the potential to slow down the virus' spread. The authors reported a significant decrease in the growth rate of the epidemic. Moreover, a corresponding increase in the doubling time of COVID-19 cases within China was observed, from 2 days (95% Confidence Interval, CI): 1.9-2.6), to 4 days (95% CI: 3.5-4.3) after lockdown. However, the authors also noted that the number of cases outside lockdown areas have increased, and new epicenters are developing across the globe.
- Pan (JAMA 2020, see ***below***) divided the epidemic in China into four periods based on key events and interventions, compared epidemiological characteristics across periods and demographic groups, and developed a susceptible-exposed-infectious-recovered model to evaluate the impact of interventions. The authors found that the effective reproductive number dropped from 3.86 (95% credible interval 3.74 to 3.97) before interventions to 0.32 (0.28 to 0.37) post interventions. The interventions were estimated to prevent 94.5% (93.7 to 95.2%) infections till February 18. They noted that at least 59% of infected cases were unascertained in Wuhan, potentially including asymptomatic and mild-symptomatic cases.
- Liu (Biology 2020, see ***below***) developed another mathematical model for the disease, which predictions emphasize the importance of major public health interventions such as isolation, quarantine, and public closings, to greatly reduce the final size of this epidemic, and make the turning point much earlier than without these measures.
- Karako (Biosci Trends 2020, see ***below***) presented a stochastic transmission model by extending the Susceptible-Infected-Removed (SIR) epidemiological model with an additional modelling of the individual action on whether to stay away from the crowded areas. The authors concluded that the infection spread in Japan would be gradually contained by reducing the time spent in the crowded zone to less than 4 hours.
- Kraemer (Science 2020, see ***below***) used real-time mobility data from Wuhan and detailed case data including travel history to elucidate the role of case importation on transmission in cities across China and ascertain the impact of control measures. The authors showed that travel restrictions are particularly useful in the early stage of an outbreak when it is confined to a certain area that acts as a major source. However, travel restrictions may be less effective once the outbreak is more widespread.
- Rong (Math Biosci Eng 2020, see ***below***) investigated the effect of delay in diagnosis on disease transmission with a new formulated dynamic model, and showed that improving the proportion of timely diagnosis and shortening the waiting time for diagnosis cannot eliminate COVID-19, but can effectively decrease the basic reproduction number and significantly reduce the transmission risk.
- Ferretti (Science 2020, see ***below***) determined requirements for case isolation and contact-tracing to stop the epidemic. The authors concluded that viral spread is too fast to be contained by manual contact tracing, but could be controlled if this process was faster, more efficient and happened at scale. A contact-tracing App which builds a memory of proximity contacts and immediately notifies contacts of positive cases can achieve epidemic control if used by enough people. The model concluded that such mobile phone App could reduce transmission enough to achieve $R < 1$ and sustained epidemic suppression, stopping the virus from spreading further. A web interface has been made available online to explore the uncertainty in the modelling assumptions (https://bdi-pathogens.shinyapps.io/covid-19-transmission-routes/).

- Sjödin (Euro Surveill 2020, see ***below***) investigated the extent of physical distancing needed to effectively control the outbreak in a lockdown situation in a small size town setting typical of Italy. The authors showed that very high adherence to community quarantine (total stay-home policy) and a small household size is necessary for curbing the outbreak in a locked-down town. The larger the household size and amount of time in the public, the longer the lockdown period needed.
- A study by Siedner (PLoS Med 2020, see ***below***) suggested that social distancing measures were associated with a statistically significant decrease in the COVID-19 case growth rate in the US. Statewide social distancing measures were also associated with a decrease in the COVID-19-attributed mortality growth rate beginning 7 days after implementation, although this decrease was no longer statistically significant by 10 days.
- The model developed by Park (Envir Res Econ 2020, see ***below***), assuming an R_0 value of 2.0 and vaccine effectiveness of 0.5, found that herd immunity would require at least 62% of the susceptible population vaccinated in South Korea.
- Considering that in the absence of vaccination, or when vaccine efficacy is poor, social distancing may help to curb the spread of diseases, Choi developed a game-theoretic epidemiological model that considers both vaccination and social distancing (J Theor Biol 2020, see ***below***).
- Block (Nat Hum Behav 2020, see ***below***) demonstrated the impact of social network-based distancing strategies.

Therapeutic interventions and research

Identifying treatment options as soon as possible is critical for the response to the COVID-19 outbreak (Lu Biosci Trends 2020, see ***below***). Various approaches, including evaluation of existing broad-spectrum antiviral drugs using standard assays, screening of a chemical library containing many existing compounds or databases, and the redevelopment of new specific drugs based on the genome and biophysical understanding of individual coronaviruses, can be used to identify potential therapies. Numerous candidates were proposed from the beginning of the epidemic, some of which were very soon administered to patients. In addition to antivirals, research and development on host-directed therapies was also recommended (Zumla Lancet 2020, see ***below***).

A list of candidate therapeutics was published by WHO in February 2020 (https://www.who.int/publications/m/item/overview-of-the-types-classes-of-candidate-therapeutics). At the same time, the Chinese Academy of Sciences suggested a list of 30 different compounds, with 12 HIV medicines, including saquinavir, indinavir, lopinavir, ritonavir and carfilzomib, two respiratory syncytial virus drugs, a schizophrenia medication and an immunosuppressant. Candidates also included certain Traditional Chinese Medicines.

Subsequent publications on this topic presented additional lists of potential compounds. For instance, a manuscript by Yan (https://www.preprints.org/manuscript/202002.0254/v1) indicated that in addition to synthetic compounds (including FDA-approved drugs), Chinese Patent Drugs (CPD) can also be a source of therapies against COVID-19. He compiled major components from 38 CPDs that are commonly used in the respiratory diseases and docked them against two drug targets, ACE2 receptor and viral main protease. Ten antiviral components, including hesperidin, saikosaponin, rutin, baicalin, glycyrrhizin, mulberroside A, puerarin, orientin, amygdalin, and ilexgenin A, were predicted as able to directly bind to both host cell target ACE2 receptor and viral target main protease, indicating their potential for treatment.

In silico work is still ongoing to identify potential drug candidates. Using network proximity analyses of drug targets and known human CoV-host interactions in the human protein-protein interactome, Zhou (Cell Discov 2020, see ***below***) computationally identified 135 putative repurposable drugs for the potential prevention and treatment of human CoV infections. In addition, 16 potential repurposable drugs (including melatonin, mercaptopurine, and sirolimus) were

further validated by enrichment analyses of drug-gene signatures and CoV-induced transcriptomics data in human cell lines. Finally, the authors presented three potential drug combinations (including sirolimus plus dactinomycin, mercaptopurine plus melatonin, and toremifene plus emodin) captured by the Complementary Exposure pattern: the targets of the drugs both hit the human CoV-host subnetwork, but target separate neighbourhoods in the human protein-protein interactome network.

As live SARS-CoV-2 handling requires high-level biosafety facilities, Fan (Chin Med J 2020, see ***below***) suggested the use of a pangolin coronavirus model to facilitate *in vitro* studies of potential drug candidates against COVID-19. The drug candidates were screened for their ability to inhibit cytopathic effect upon GX_P2V/pangolin/2017/ Guangxi strain infection of Vero E6 cells. The approach identified cepharanthine, selamectin and mefloquine hydrochloride as potential drugs.

In another example, Gordon (Nature 2020, see ***below***) presented a SARS-CoV-2 protein interaction map providing another approach to the identification of targets for drug repurposing. The authors cloned, tagged and expressed 26 of the 29 SARS-CoV-2 proteins in human cells and identified the human proteins that physically associated with each of the SARS-CoV-2 proteins using affinity-purification mass spectrometry, identifying 332 high-confidence protein-protein interactions between SARS-CoV-2 and human proteins. Among these, 66 druggable human proteins or host factors targeted by 69 compounds were identified (of which, 29 drugs are approved by the US FDA, 12 are in clinical trials and 28 are preclinical compounds). Two sets of pharmacological agents that displayed antiviral activity were found: inhibitors of mRNA translation and predicted regulators of the sigma-1 and sigma-2 receptors.

As early as in February 2020, a publication in Nature (Maxmen 2020, see ***below***) reported the launch of more than 80 clinical trials to test candidate coronavirus treatments. However, as illustrated by the Global Coronavirus COVID-19 Clinical Trial Tracker (https://www.covid-trials.org/), this number quickly increased to close to 2000. A list and classification of COVID-19 experimental treatments has been made available by WHO on April 28 (https://www.who.int/publications/m/item/covid-19-candidate-treatments). A more recent overview of the advancement of candidate therapeutics, with classification by mode of action, can be found at https://www.racap.com/media/Covid-19/COVID-19_TX_10232020_F.pdf?v=0JDeeRgx6286WufrJxh_Cm1PquJVqf2KdCM4-vk2f38.

Management of early symptoms

The French minister, Oliver Veran, tweeted on March 14th that people with suspected COVID-19 should avoid anti-inflammatory drugs. “Taking anti-inflammatory drugs (**ibuprofen**, cortisone . . .) could be an aggravating factor for the infection. If you have a fever, take paracetamol,” he said. His comments seem to have stemmed in part from remarks attributed to an infectious diseases doctor in south west France (Day BMJ 2020, see ***below***). She was reported to have cited four cases of young patients with covid-19 and no underlying health problems who went on to develop serious symptoms after using non-steroidal anti-inflammatory drugs (NSAIDs) in the early stage of their symptoms. Some experts in the UK backed this sentiment that for treating symptoms such as fever and sore throat, it seems sensible to stick to paracetamol as first choice. In parallel, the EMA stated that there is currently no scientific evidence establishing a link between ibuprofen and worsening of COVID-19 (https://www.ema.europa.eu/en/news/ema-gives-advice-use-non-steroidal-anti-inflammatories-covid-19). An overview by Sodhi (Chest 2020, see ***below***) confirmed that the current epidemiological evidence is not strong enough to infer a causal link of a harmful effect of ibuprofen in patients with COVID-19. A review by Smart (Inflammopharmacology 2020, see ***below***) indicated that double-blind, placebo-controlled study results are still required regarding the use of ibuprofen in COVID-19 patients. The authors noted that limited studies have suggested: (i) no direct interactions between ibuprofen and SARS-CoV-2 and (ii) there is no evidence to suggest ibuprofen affects the regulation of ACE2 in human studies. Furthermore, *in vitro* studies suggest ibuprofen may facilitate cleavage of ACE2 from the membrane, preventing membrane-dependent viral entry into the cell, the clinical significance of which is uncertain. Additionally, *in vitro* evidence suggests that inhibition of the

transcription factor nuclear factor-κB (NF-kB) by ibuprofen may have a role in reducing excess inflammation or cytokine release in COVID-19 patients. Finally, there is no evidence that ibuprofen will aggravate or increase the chance of infection of COVID-19. A prospective cohort study recently reported by Abu Esba (manuscript on Research Square: https://www.researchsquare.com/article/rs-85148/v1) concluded that ibuprofen and other NSAID acute or chronic use were not associated with worse COVID-19 disease outcomes.

Antiviral drugs

Various antiviral drug candidates have been rapidly assessed in COVID-19 patients. However, as of today, the outcome of only a limited number of randomized controlled trials is available, and the search for a safe and efficacious treatment of COVID-19 is still ongoing.

Inhibitors of virus entry

Chloroquine, hydroxychloroquine and analogues

Chloroquine and its structural analogues such as hydroxychloroquine, amodiaquine, pamaquine, plasmoquine, primaquine, mefloquine or ferroquine, have been used for decades as the primary and most successful drugs against malaria (Al-Bari Pharmacol Res Perspect 2017, see ***below***). These drugs are also found to be effective against a wide variety of viral infections. Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV (Wang Cell Res 2020, see ***below***). Besides its antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect *in vivo*. Chloroquine is widely distributed in the whole body, including lung, after oral administration. Devaux (Int J Antimicr Ag 2020, see ***below***) recently provided an overview of the possible mechanisms of chloroquine interference with SARS-CoV-2 replication.

Of note, several clinical studies of chloroquine and its analogues have been conducted for treatment of dengue, hepatitis C virus, chikungunya and HIV-1 infections. Disappointingly, the outcome of one of these clinical trials showed no benefit of chloroquine treatment of dengue virus infection (Tricou PLoS Negl Trop Dis 2010, see ***below***). More recently, Garbern (Open For Inf Dis 2019, see ***below***) found a non-statistically significantly decreased risk of mortality in Ebola patients exposed to artesunate-amodiaquine during mass drug administrations as compared with Ebola patients not exposed to artesunate-amodiaquine.

A comprehensive review by Morrisette (Inf Dis Ther 2020, see ***below***), published on August 1st 2020, described the current understanding of hydroxychloroquine and its use against SARS-CoV-2 infection, and discussed remaining knowledge gaps.

Preclinical data

Chloroquine was found to potently inhibit infection of Vero E6 cells by a SARS-CoV-2 clinical isolate (EC50 = 1.13 µM; CC50 > 100 µM, SI > 88.50). The drug was shown to function at both entry, and at post-entry stages of the SARS-CoV-2 infection in Vero E6 cells. The EC90 value of chloroquine against SARS-CoV-2 was 6.90 µM, which can be clinically achievable as demonstrated in the plasma of rheumatoid arthritis patients who received 500 mg administration.

Yao (Clin Inf Dis 2020, see ***below***) found hydroxychloroquine (EC50=0.72 µM) to be more potent than chloroquine (EC50=5.47 µM) *in vitro*. Based on physiologically-based pharmacokinetic models results, a loading dose of 400 mg twice daily of hydroxychloroquine sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days would be recommended for SARS-CoV-2 infection, as it reached three times the potency of chloroquine phosphate when given 500 mg twice daily 5 days in advance. Similar results were reported by Liu (Cell Discov 2020, see ***below***). At all conditions tested (MOI of 0.01, 0.02, 0.2, and 0.8), the EC50 for chloroquine (2.71, 3.81, 7.14, and 7.36 µM) was lower than that of hydroxychloroquine (4.51, 4.06, 17.31, and 12.96 µM). The differences in EC50 values were statistically significant at an MOI of 0.01 ($P < 0.05$) and MOI of 0.2 ($P < 0.001$).

On May 6 2020, Maisonnasse (manuscript on Research Square: https://www.researchsquare.com/article/rs-27223/v1) reported the antiviral activity of hydroxychloroquine both *in vitro* and in SARS-CoV-2-infected macaques. Hydroxychloroquine showed antiviral activity in African green monkey kidney (Vero E6) cells, but not in a model of reconstituted human airway epithelium. In macaques, the authors tested different treatment strategies in comparison to placebo, before and after peak viral load, alone or in combination with azithromycin. Neither hydroxychloroquine nor hydroxychloroquine + azithromycin showed a significant effect on the viral load levels in any of the tested compartments. When the drug was used as a pre-exposure prophylaxis, hydroxychloroquine did not confer protection against acquisition of infection.

Clinical data

Cortegiani (J Crt Care 2020, see ***below***) identified 23 clinical trials in China evaluating the efficacy and safety of chloroquine or hydroxychloroquine in the treatment of COVID-19 associated pneumonia. The trials varied in study design, severity of the disease in the target population and in dosing and duration of the treatment (as illustrated in March 2020 by Li Nature, see ***below***). The first results, from more than 100 patients, were released by the China National Centre for Biotechnology Development and said to indicate that chloroquine phosphate is superior to control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course, according to a news briefing (Gao BioSci Trends 2020, see ***below***). Severe adverse reactions to chloroquine phosphate were not noted in the aforementioned patients.

In order to guide and regulate the use of chloroquine in patients with COVID-19, the "multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia" recommended chloroquine phosphate tablet, 500mg twice per day for 10 days for patients diagnosed as mild, moderate and severe cases of novel coronavirus pneumonia and without contraindications to chloroquine (Zhonghua Jie He He Hu Xi Za Zhi 2020, see ***below***).

The Dutch CDC suggested to treat severe infections requiring admission to the hospital and oxygen therapy or admitted to the ICU, with chloroquine (Cortegiani J Crt Care 2020, see ***below***). However, the document also stated that treating patients only with optimal supportive care is still a reasonable option, due to lack of supportive evidence. The suggested regimen in adults consists of 600mg of chloroquine base followed by 300mg after 12 h on day 1, then 300mg × 2/die per os on days 2–5.

Huang (J Mol Cell Biol 2020, see ***below***) reported the outcome of a small randomized trial that compared a group of 10 patients, including 3 severe and 7 moderate cases, treated with chloroquine 500mg orally twice-daily for 10 days to another group of 12 patients, including 5 severe and 7 moderate cases, treated with lopinavir/ritonavir 400/100mg orally twice-daily for 10 days. Compared to the lopinavir/ritonavir group, the percentages of patients who became SARS-CoV-2 negative in the chloroquine group were slightly higher at Day 7, Day 10, and Day 14. Patients treated with chloroquine were also discharged from hospital more rapidly. The data therefore point to a superior efficacy of chloroquine. However, larger studies remain needed before solid conclusions on this topic can be drawn.

In addition, Gautret (International Journal of Antimicrobial Agents 2020, see ***below***) reported the outcome of an open-label non-randomized clinical trial that evaluated hydroxychloroquine alone or combined with azithromycin compared to untreated patients from another centre and cases refusing the protocol. Twenty cases received treatment in this study and showed a significant reduction of the viral carriage at day 6 post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination. A second open-label trial of the combination of hydroxychloroquine and azythromycin in 80 patients was also reported by the same team (Gautret Trav Med Inf Dis 2020, see ***below***).

Geleris (NEJM 2020, see ***below***) evaluated the association between hydroxychloroquine use and intubation or death at a large medical center in an observational study in New York City. Of 1376 patients included in the study, 811 received hydroxychloroquine (600 mg twice on day 1, then 400 mg daily for a median of 5 days); 45.8% of the patients were treated within 24 hours after presentation to the emergency department, and 85.9% within 48 hours. Hydroxychloroquine-treated patients were more severely ill at baseline than those who did not receive hydroxychloroquine. Overall, 346 patients (25.1%) had a primary end-point event (180 were intubated, 66 died after intubation, and 166 died without intubation). In the main analysis, there was no significant association between hydroxychloroquine use and intubation or death (hazard ratio, 1.04, 95% confidence interval, 0.82 to 1.32). Results were similar in multiple sensitivity analyses.

Another registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19 was presented by Mehra (Lancet 2020, see ***below***). The registry comprised data from patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory finding for SARS-CoV-2. Of a total of 96032 patients included, 14 888 patients were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with a macrolide, 3016 received hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and 81 144 patients were in the control group. After controlling for multiple confounding factors, when compared with mortality in the control group (9.3%), hydroxychloroquine (18.0%; hazard ratio 1.335, 95% CI 1.223–1.457), hydroxychloroquine with a macrolide (23.8%; 1.447, 1.368–1.531), chloroquine (16.4%; 1.365, 1.218–1.531), and chloroquine with a macrolide (22.2%; 1.368, 1.273–1.469) were each independently associated with an increased risk of in-hospital mortality. In conclusion, the authors were unable to confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcomes for COVID-19. They also noted that the study had several limitations and that the association of decreased survival with hydroxychloroquine or chloroquine treatment regimens should be interpreted cautiously. Importantly, after publication of this paper, several concerns were raised with respect to the veracity of the data and analyses conducted. As an independent third-party peer review could not be conducted, Mehra and 2 other co-authors requested that the paper be retracted (Mehra Ruschitzka and Patel, Lancet 2020, see ***below***).

Perinel (Clin Inf Dis 2020, see ***below***) reported the outcome of a preliminary PK study to define the optimal dosing regimen for COVID-19 patients in ICU. Based on the authors' simulations, a loading dose of 800 mg once daily on day 1, followed by 200 mg twice daily for 7 days was proposed. Therapeutic drug monitoring was also recommended to personalize the optimal dosing regimen, as well as additional PK and PD (virological) studies.

Garcia-Cremades (Clin Pharmacol Ther 2020, see ***below***) further investigated the topic of hydrochloroquine dosing, using available data. The authors predicted that higher hydroxychloroquine daily doses (e.g. as high as 800 mg BID), were associated with rapid rates of viral decline and increased the percentage of PCR negative patients, but could result in increased risk of QTc prolongation (indicator of delayed ventricular repolarisation as measured by electrocardiogram).

Borba (JAMA Netw Open 2020, see ***below***) presented interim results from a double-masked, randomized, phase IIb clinical trial in adult patients hospitalized with severe disease to evaluate high vs. low dose chloroquine diphosphate. Data from 81 patients were analysed. The authors concluded that the higher chloroquine dosage should not be recommended for critically ill patients with COVID-19 because of its potential safety hazards, especially when taken concurrently with azithromycin and oseltamivir. However, a report based on data from the U.S. FDA's Adverse Event Reporting System (FAERS) concluded that (hydroxy)chloroquine use was not associated with a safety signal (Sarayani Res Social Adm Pharm 2020, see ***below***). Azithromycin used alone was associated with TdP/QT prolongation events.

On March 28th, the U.S. FDA issued an emergency use authorization (EUA) that allowed for chloroquine phosphate and hydroxychloroquine sulfate donated to the Strategic National Stockpile to be used to treat certain hospitalized patients

with COVID-19 when a clinical trial was unavailable, or participation in a clinical trial was not feasible. However, new information, including clinical trial data results, led to the conclusion that this drug may not be effective to treat COVID-19 and that the drug's potential benefits for such use do not outweigh its known and potential risks. The authorization was thus revoked on June 15th 2020 (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and). On July 4th, the WHO discontinued the hydroxychloroquine arm in the Solidarity trial as interim results of the trial showed little or no reduction in the mortality of hospitalized COVID-19 patients when compared to standard of care (https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19).

A review by Rakedzon (Rambam Maimonides Med J 2020, see ***below***) included 17 studies evaluating hydroxychloroquine treatment. A total of 13 were observational studies, and 4 were randomized controlled trials. In terms of effect on mortality rates, observational studies provided conflicting results. As a whole, randomized controlled trials, including one large British randomized controlled trial that has not yet been published, showed no significant effect of hydroxychloroquine on mortality rates, clinical cure, and virologic response.

Boulware (NEJM 2020, see ***below***) reported the outcome of a randomized, double-blind, placebo-controlled trial across the United States and parts of Canada testing hydroxychloroquine (used within 4 days after exposure) as **post-exposure prophylaxis**. The study enrolled 821 asymptomatic participants. Overall, 87.6% of the participants (719 of 821) reported a high-risk exposure to a confirmed COVID-19 contact. The incidence of new illness compatible with COVID-19 did not differ significantly between participants receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]); the absolute difference was −2.4 percentage points (95% confidence interval, −7.0 to 2.2; P=0.35). Side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported.

Hydroxychloroquine has also been considered for **pre-exposure prophylaxis** against COVID-19. Several randomized, double-blind, controlled studies to evaluate the effectiveness and safety of hydroxychloroquine for prophylaxis of COVID-19 have been reported as ongoing. For instance, a trial with chloroquine phosphate or hydroxychloroquine sulphate in 40 000 healthcare workers in the UK (https://clinicaltrials.gov/ct2/show/NCT04303507?term=healthy+coronavirus&recrs=abdf&type=Intr&draw=2&rank=11), a trial in Mexico in 400 health care workers receiving hydroxychloroquine (https://clinicaltrials.gov/ct2/show/NCT04318015?term=healthy+coronavirus&recrs=abdf&type=Intr&draw=2&rank=20), or in Thailand, a trial in 40 000 healthcare workers in a healthcare facility delivering direct care to patients (https://clinicaltrials.gov/ct2/show/NCT04303507?term=healthy+coronavirus+chloroquine&recrs=abdf&type=Intr&draw=2&rank=1).

Additional data of interest

Data reported by Ou on July 22 (manuscript on bioRxiv, see: https://www.biorxiv.org/content/10.1101/2020.07.22.216150v1) provided a mechanistic explanation for the disappointing *in vivo* data of hydroxychloroquine as a treatment for COVID-19. The authors showed that the SARS-CoV-2 entry process is more dependent than that of SARS-CoV-1 on TMPRSS2 expression. Moreover, it was demonstrated that hydroxychloroquine efficiently blocks viral entry mediated by cathepsin L, but not by TMPRSS2, and that a combination of hydroxychloroquine and a clinically-tested TMPRSS2 inhibitor prevents SARS-CoV-2 infection more potently than either drug alone.

Umifenovir (arbidol)

Umifenovir (arbidol), first developed by the Russian Research Chemical-Pharmaceutical Institute, could effectively inhibit SARS-CoV-2 infection at a concentration of 10-30 µM in vitro (Fang Front Pharmacol 2020, see ***below***). This

suggests that umifenovir may have the ability to inhibit SARS-CoV-2 *in vivo*, making it a promising therapeutic drug for COVID-19. According to a communication of the China National Center for Biotechnology Development at a press conference, the drug has been added to the list of possible treatments of COVID-19 in the sixth edition of the treatment and diagnosis plan published by the Chinese National Health Commission (https://www.thestar.com.my/news/regional/2020/02/18/chinese-experts-confirm-antimalarial-drug-is-effective-on-covid-19-infection).

Deng (J Inf 2020, see ***below***) presented the results of a small retrospective cohort study in 33 adults with laboratory-confirmed COVID-19 without invasive ventilation. The authors concluded that combined oral umifenovir (at a dose of 200mg every 8 h) and lopinavir/ritonavir therapy was associated with a significant elevated negative conversion rate of COVID-19 RT-PCR at 7-day and 14-day, compared with lopinavir/ritonavir only. The combination therapy was also associated with a significantly improved the chest CT scans at the 7-day timepoint.

A non-randomized clinical study that compared umifenovir to lopinavir/ritonavir in 50 patients concluded in the superiority of umifenovir. Patients in the umifenovir group had a shorter duration of positive RNA test compared to those in the lopinavir/ritonavir group (P<0.01) (Zhu J Inf 2020, see ***below***).

Lian (Clin Microbiol Infect 2020, ***below***) reported a retrospective study in COVID-19 confirmed patients, with 45 having received arbidol and 36 in control group. 73.3% patients in umifenovir group were tested negative in SARS-CoV-2 within 7 days after admission; 77.8% in control group (p=0.19). The median time from onset of symptoms to SARS-CoV-2 turning negative were 18 days (interquartile range [IQR] 12-21) in umifenovir group and 16 days (IQR, 11-21) in control group (p= 0.42). Patients in arbidol group had longer hospital stay than patients in control group (13 days [IQR, 9-17] vs 11 days [IQR, 9-14], p=0.04). No deaths or severe adverse reaction were found in any groups.

A review by Huang (J Med Virol 2020, see ***below***) in July 2020 identified a total of 12 studies of umifenovir with 1052 COVID-19 patients. Compared with control group, umifenovir was associated with higher negative rate of PCR on day 14 (RR:1.27; 95% CI: 1.04 to 1.55). However, umifenovir was not related to nucleus acid negative conversion time (MD: 0.09; 95% CI: −1.48 to 1.65), negative rate on day 7 (RR:1.09; 95% CI: 0.91 to 1.31), incidence of composite endpoint (RR:1.20; 95% CI: 0.61 to 2.37), rate of fever alleviation on day 7 (RR:1.00; 95% CI: 0.91 to 1.10), rate of cough alleviation on day 7 (RR:1.00; 95% CI: 0.85 to 1.18), or hospital length of stay (MD: 1.34; 95% CI: ‐2.08 to 4.76). Additionally, umifenovir was safe in COVID-19 patients (RR for incidence of adverse events: 1.29; 95% CI: 0.57 to 2.92). The results of sensitivity analysis and subgroup analysis were similar to pooled results. There was no evidence to support the use of umifenovir for improving patient-important outcomes in patients with COVID-19.

Teicoplanin

Teicoplanin, a glycopeptide antibiotic routinely used in the clinic to treat bacterial infection with low toxicity, had been previously reported to significantly inhibit the invasion of cells by Ebola virus, SARS-CoV and MERS-CoV, via specific inhibition of the activity of cathepsin L. The efficacy of teicoplanin against SARS-CoV-2 infection was recently tested: teicoplanin was found to potently prevent the entrance of S-HIV luc pseudoviruses into the cytoplasm, with an IC50 of 1.66 μM. Although the inhibitory effect upon replication of wildtype viruses *ex vivo* and *in vivo* remains to be determined, these preliminary result support a potential antiviral activity of teicoplanin (Zhang on BioRixv: https://www.biorxiv.org/content/10.1101/2020.02.05.935387v1).

Nafamostat

Nafamostat, an anticoagulant, is a potent inhibitor of MERS-CoV, preventing membrane fusion. The drug has been found inhibitive against SARS-CoV-2 *in vitro* infection (EC50 = 22.50 μM, CC50 > 100 μM, SI > 4.44) (Wang Cell Res 2020, see ***below***).

EK1

Peptide OC43-HR2P, derived from the HR2 domain of human CoV OC43, has been shown to exhibit broad fusion inhibitory activity against multiple human CoVs. EK1, the optimized form of OC43-HR2P, showed substantially improved pan-CoV fusion inhibitory activity and pharmaceutical properties (Xia Sci Adv 2019, see ***below***). Crystal structures indicated that EK1 can form a stable six-helix bundle structure with both short α-HCoV and long β-HCoV HR1s, further supporting the role of HR1 region as a viable pan-CoV target site. Intranasal application of EK1 peptide before or after viral challenge protected human DPP4-transgenic mice from MERS-CoV infection (Jiang Em Micr Inf 2020, see ***below***).

Xia (Cell Res 2020, see ***below***) subsequently generated a series of lipopeptides derived from EK1 and found that **EK1C4** was the most potent fusion inhibitor against SARS-CoV-2 S protein-mediated membrane fusion and pseudovirus infection with IC50s of 1.3 and 15.8 nM, about 241- and 149-fold more potent than the original EK1 peptide, respectively. EK1C4 was also highly effective against membrane fusion and infection by other human CoV pseudoviruses. Intranasal application of EK1C4 before or after challenge with HCoV-OC43 protected mice from infection.

Niclosamide

Niclosamide, an FDA-approved anthelminthic drug, was found to be effective against various viral infections with nanomolar to micromolar potency such as SARS-CoV, MERS-CoV, Zika virus, hepatitis C virus and human adenovirus, indicating its potential activity against SARS-CoV-2 (Xu ACS Infect Dis 2020, see ***below***). However, experimental data with SARS-CoV-2 have not been reported yet.

Baricitinib

Using an Artificial Intelligence-derived knowledge graph, queried by a suite of algorithms, Stebbing (Lancet Inf Dis 2020, see ***below***) also identified a group of approved drugs that could inhibit clathrin-mediated endocytosis and thereby inhibit viral infection of cells. The drug targets are members of the numb-associated kinase (NAK) family, including the AP2-associated protein kinase 1 (AAK1) and GAK, the inhibition of which has been shown to reduce viral infection *in vitro*. Baricitinib was identified as a NAK inhibitor. Baricitinib also binds the cyclin G-associated kinase, another regulator of endocytosis. Further, baricitinib is a potent and selective JAK inhibitor and powerful anti-inflammatory. Because the plasma concentration of baricitinib on therapeutic dosing (either as 2 mg or 4 mg once daily) is sufficient to inhibit AAK1, Richardson (Lancet, see ***below***) suggested it could be trialled, using an appropriate patient population with COVID-19 acute respiratory disease (see ***JAK-STAT inhibitors*** below for information on clinical trials of baricitinib).

Camostat mesylate

The *in vitro* data reported by Hoffmann (Cell 2020, see ***below***) suggested that the Japanese drug camostat mesylate (trade name: Foipan), a TMPRSS2 inhibitor, might constitute a treatment option for COVID-19. The drug is currently evaluated in various randomized controlled trials (e.g. NCT04353284 or NCT04321096).

RNA-dependent RNA polymerase inhibitors

Nucleoside analogues commonly target viral replication, particularly the viral DNA or RNA polymerase, and have succeeded clinically in treating multiple viral infections (Agostini mBio 2018, see ***below***). However, identification and development of antiviral nucleosides against coronaviruses have been hampered by the presence of the unique CoV proofreading 3'-5'exoribonuclease (ExoN). While nucleoside analogues such as BCX4430 inhibit CoVs, several previously tested nucleoside analogues have been incapable of potently inhibiting CoV replication, and others have demonstrated poor selectivity indexes. CoV resistance to the mutagens 5-fluorouracil and ribavirin *in vitro* is attributed to their removal by the proofreading ExoN, supporting the hypothesis that an effective nucleoside analogue must evade proofreading to successfully interfere with CoV RNA synthesis.

Remdesivir

Remdesivir (GS-5734) is the monophosphoramidate prodrug of the C-adenosine nucleoside analogue GS-441524 (Agostini mBio 2018, see ***below***). This drug candidate had been shown to inhibit *in vitro* infections with SARS-CoV, MERS-CoV, and bat CoV strains that are capable of replicating in primary human airway epithelial cells and mediate entry using human CoV receptors. Remdesivir (EC50 = 0.77 µM; CC50 > 100 µM; SI > 129.87) potently blocked infection of Vero E6 cells by a clinical isolate of SARS-CoV-2 at low-micromolar concentration and showed high selectivity index[16] (Wang Cell Res 2020, see ***below***).

In vivo, remdesivir demonstrated both prophylactic and therapeutic efficacy against SARS-CoV disease in a mouse model. In a Ces1c-/- hDPP4 mouse model of MERS-CoV infection, both prophylactic and therapeutic use of remdesivir improved pulmonary function and reduced lung viral loads and severe lung pathology (Sheahan Nat Commun 2020, see ***below***). Therapeutic remdesivir treatment 12h post-inoculation with MERS-CoV resulted in reduction in clinical signs, reduced virus replication in the lungs, and decreased presence and severity of lung lesions (de Wit PNAS 2020, see ***below***).

Remdesivir inhibits murine hepatitis virus (MHV) with similar 50% effective concentration values (EC50) as SARS-CoV and MERS-CoV (Agostini mBio 2018, see ***below***), and this model was used to assess virus resistance to remdesivir. Passage of wild type MHV in the presence of the remdesivir parent nucleoside selected two mutations in the nsp12 polymerase at residues conserved across all CoVs that conferred up to 5.6-fold resistance to remdesivir, as determined by EC50. The resistant viruses were unable to compete with wild type virus in direct coinfection passage in the absence of remdesivir. Introduction of the MHV resistance mutations into SARS-CoV resulted in the same *in vitro* resistance phenotype and attenuated SARS-CoV pathogenesis in a mouse model. Finally, an MHV mutant lacking ExoN proofreading was found significantly more sensitive to remdesivir. Combined, the results indicate that remdesivir interferes with the nsp12 polymerase even in the setting of intact ExoN proofreading activity and that resistance can be overcome with increased, nontoxic concentrations of the drug candidate.

An overview of the various arguments supporting the use of remdesivir to treat COVID-19 has also been made available by Ko in March 2020 (Int J Antimicrob Ag, see ***below***). A review of available data as well as (ongoing) clinical trials has also been published by Frediansyah (Clin Epid Glob Health 2020, see ***below***).

The first randomized, double-blind, placebo-controlled, multicenter clinical trial was reported on April 29, 2020 (Wang Lancet 2020, see ***below***). The study was conducted in China with 237 patients (158 in the remdesivir group and 79 in the placebo control group; NCT04257656), and the primary endpoint was the time taken to achieve clinical improvement. The study revealed that treatment with remdesivir did not lead to a significant reduction in the time taken to achieve clinical improvement. In addition, mortality and viral clearance time in patients with severe COVID-19 were not significantly different from those in the placebo group, suggesting that remdesivir had poor clinical benefits. Another phase 3 randomized controlled trial (NCT04252664) conducted in China was terminated prematurely. It has been mentioned that remdesivir (100 mg dose except for the first day of 200 mg) for ten days may raise safety concerns in China due to differences in ethnicity (Zhang, Huang et al. J Med Vir 2020, see ***below***).

Another phase 3 double-blind, randomized, placebo-controlled trial of the drug, the Adaptive COVID-19 Treatment Trial (ACTT, NCT04280705) enrolled patients in the U.S., Europe and Asia. A total of 1063 patients underwent randomization (Beigel NEJM 2020, see ***below***). The data and safety monitoring board recommended early unblinding of the results on the basis of findings from an analysis that showed shortened time to recovery in the remdesivir group. Preliminary results from the 1059 patients (538 assigned to remdesivir and 521 to placebo) with data available after randomization indicated that those who received remdesivir had a median recovery time of 11 days (95% confidence

[16] Importantly, in the same study, high concentrations of three nucleoside analogs including ribavirin, penciclovir and favipiravir were required to reduce viral infection

interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%).

In addition, Gilead announced the results of the phase 3 trial of remdesivir from the open-label, Phase 3 SIMPLE trial evaluating 5-day and 10-day dosing durations of the antiviral in hospitalized patients with severe manifestations of COVID-19. The study is being conducted at 180 trial sites around the world, including sites in the United States, China, France, Germany, Hong Kong, Italy, Japan, Korea, the Netherlands, Singapore, Spain, Sweden, Switzerland, Taiwan and the United Kingdom. The data that were disclosed demonstrated that patients receiving a 10-day treatment course of remdesivir achieved similar clinical improvement compared with those taking a 5-day treatment course. No new safety signals were identified with remdesivir across either treatment group. Clinical outcomes varied by geography. In an exploratory analysis, patients in the study who received remdesivir within 10 days of symptom onset had improved outcomes compared with those treated after more than 10 days of symptoms (https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-covid-19).

Grein (NEJM 2020, see ***below***) analysed the data of patients hospitalized for severe COVID-19 who were treated with compassionate-use remdesivir in the U.S., Europe, Canada, and Japan. Clinical improvement was observed in 36 of 53 patients (68%). Mortality reached 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.

A review of available clinical data by Brouqui (New Microbes New Infect 2020, see ***below***), published online in June 2020, concluded that it was far too premature to identify remdesivir as a curative or life-saving intervention against COVID-19. Nevertheless, the U.S. FDA authorized the emergency use of remdesivir (Veklury) for treatment of COVID-19 on May 1st 2020 (https://www.fda.gov/media/137564/download). On August 31st, expanded emergency use authorisation (EUA) was granted by the US FDA for treating not only hospitalised patients suffering from severe COVID-19, but also those who are moderately afflicted.

While clinical trials of remdesivir are still ongoing, Doggrell (Expert Opin Investig Drugs 2020, see ***below***) recently concluded that we still need to determine whether remdesivir is a game-changing remedy or a ripple in the ongoing search for a medicine for the treatment of COVID-19.

Ribavirin

I*n vitro* data have not identified ribavirin as a lead candidate for COVID-19 treatment. However, a randomized clinical trial of the drug used in combination with pegylated interferon for COVID-19 has been reported in China (ChiCTR2000029387, Li Nat Rev Drug Discov 2020, see ***below***). (Zhang, Huang et al. (J Med Vir 2020, see ***below***) indicated in March 2020 that ribavirin was indicated for the general treatment of COVID-19 in Chinese treatment guidelines, and combination with interferon recommended. However, their clinical safety and efficacy against COVID-19 were not evaluated in China.

Favipiravir

Randomized trials of favipiravir have been reported in China for COVID-19 therapy (ChiCTR2000029544, ChiCTR2000029600, Li Nat Rev Drug Discov 2020, see ***below***). On March 17, Zhang Xinmin released in the media data from a Chinese trial that evaluated favipiravir (http://www.chinadaily.com.cn/a/202003/17/WS5e708666a31012821727fcbd.html)**.** The Third People's Hospital of Shenzhen in Guangdong province conducted a clinical trial on 80 patients, with 35 receiving the drug. The results

showed that patients treated with favipiravir took four days before being tested negative, whereas the control group took 11 days. The lung conditions of 91.43 percent of the treated group improved as shown in chest imaging, compared with 62.22 percent of the control group. In another comparative trial on 120 patients conducted by Zhongnan Hospital of Wuhan University, the results were said to have shown that the treated group had a higher recovery rate at the end of treatment and took less time to reduce fever and relieve cough. A number of other clinical trials followed in other countries. Joshi (Int J Inf Dis 2020, see ***below***) very recently reviewed available information on favipiravir and COVID-19.

Other RNA-dependent RNA polymerase inhibitors

As reviewed by Al-Horani (Viruses 2020, see), **galidesivir**, an adenosine nucleoside analogue, is an active site inhibitor of RdRp (EC50 < 50 µM). Similar to remdesivir, it is a prodrug that is metabolized by cellular kinases to the corresponding active form of nucleoside triphosphate. The triphosphate form binds to the active site of the viral enzyme and gets incorporated into the growing viral RNA chain resulting in premature chain termination. The drug is being tested in a phase 1 clinical trial for COVID-19 or Yellow Fever in Brazil in collaboration with the U.S. NIAID (NCT03891420; n = 132).

Clevudine, a thymidine nucleoside analogue, was approved in Korea for the treatment of hepatitis B virus infection. It is a prodrug that requires phosphorylation to form the corresponding active nucleotide, the triphosphate. Mechanistically, the triphosphate active form appears to non-competitively inhibit the HBV reverse transcriptase protein priming and DNA synthesis. Importantly, although clevudine showed a potent antiviral response, its long-term use for more than a year led to the development of viral resistance and myopathy. The drug is being evaluated in a phase 2 as a treatment for COVID-19 in Korea (NCT04347915; n = 60).

Emtricitabine and tenofovir disoproxil have been reported by a recent computational work as potential inhibitors of RdRp of SARS-CoV-2. The efficacy of emtricitabine and tenofovir disoproxil as a prophylactic combination against SARS-CoV-2 infection is being evaluated in a large randomized, double-blind, controlled with placebo clinical trial for health care providers exposed to COVID-19 patients (NCT04334928). The efficacy of **emtricitabine and tenofovir alafenamide** as a prophylactic combination against SARS-CoV-2 infection is also to be evaluated in a planned large randomized, double-blind, controlled phase 3 trial for health care providers exposed to COVID-19 patients (NCT04405271; n = 1378).

Alternative RNA polymerase inhibitors have been described. For instance, Lung (J Med Vir 2020, see ***below***) screened chemical structures from traditional Chinese medicinal compounds proven to show anti-viral activity in SARS-CoV and similar chemical structures through a molecular docking study to target the RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2, SARS-CoV and MERS-CoV. **Theaflavin** was identified as a SARS-CoV-2 RdRp inhibitor (Mhatre Phytomed 2020, see ***below***). The potential of this compound remains to be experimentally confirmed.

Protease inhibitors

Involved in the formation of the coronavirus replication complex, the viral main protease (3-chymotrypsin-like cysteine protease, 3CLpro, also called Mpro) represents an attractive target for therapy. The structure of Mpro has been resolved and made publicly available to facilitate global efforts to develop novel drug candidates. Chen (F1000Res 2020, see ***below***) prepared the three-dimensional model of the SARS-CoV-2 3CL pro using the crystal structure of the highly similar (96% identity) ortholog from SARS-CoV. All residues involved in the catalysis, substrate binding and dimerisation were found 100% conserved. Comparison of the polyprotein PP1AB sequences showed 86% identity. The 3C-like cleavage sites on the coronaviral polyproteins appeared highly conserved.

Lopinavir/ritonavir

Lopinavir and ritonavir, which are used as a combination therapy for the treatment and prevention of HIV/AIDS, soon appeared as candidate of choice for COVID-19 therapy. Yao (J Med Vir 2020, see ***below***) reviewed the literature on the efficacy of lopinavir *in vitro* and *in vivo*, especially in patients with SARS and MERS. Lin (manuscript on medRxiv:

https://www.biorxiv.org/content/10.1101/2020.01.31.929695v2) presented evidence supporting the mode of action of lopinavir, ritonavir and dapunavir through their predicted interactions with SARS-CoV-2 proteases. The authors suggested that the therapeutic effect of ritonavir and lopinavir on COVID-19 may be mainly due to their inhibitory effect on coronavirus endopeptidase C30, with ritonavir appearing to have stronger efficacy; the inhibitory effect of darunavir on SARS-CoV-2 and its potential therapeutic effect may be mainly due to its inhibitory effect on papain-like viral protease.

Several clinical trials evaluated lopinavir and/or ritonavir (± other drug candidates) in COVID-19. Li for instance reported that in study NCT04252885, lopinavir/ritonavir presented little benefit over supportive care for improving the clinical outcome of patients hospitalized with mild/moderate COVID-19 (Med NY 2020, see ***below***).

Cao (NEJM 2020, see ***below***) reported the outcome of an open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection in Wuhan. 199 patients were randomly assigned in a 1:1 ratio to receive either lopinavir-ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone. Treatment with lopinavir-ritonavir was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90 to 1.72). Mortality at 28 days was similar in the lopinavir-ritonavir group and the standard-care group (19.2% vs. 25.0%; difference, -5.8 percentage points; 95% CI, -17.3 to 5.7). The percentages of patients with detectable viral RNA at various time points were similar. Moreover, lopinavir-ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events. The interpretation of these data in the editorial by Baden (NEJM 2020, see ***below***) is also of interest. For instance, it highlighted the fact that patients recruited for this study were late in infection and already had considerable tissue damage.

On July 4th, from the analysis of interim data from the trial, the WHO discontinued the lopinavir/ritonavir arm of the Solidarity trial (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments).

In the Recovery trial in the UK (NCT04381936), 1616 patients were randomly allocated to receive lopinavir–ritonavir and 3424 patients to receive usual care (Recovery collaborative group Lancet 2020: see ***below***). Overall, 374 (23%) patients allocated to lopinavir–ritonavir and 767 (22%) patients allocated to usual care died within 28 days (rate ratio 1·03, 95% CI 0·91–1·17; p=0·60). Results were consistent across all prespecified subgroups of patients. Among patients not on invasive mechanical ventilation at baseline, there was no significant difference in the proportion who met the composite endpoint of invasive mechanical ventilation or death (risk ratio 1·09, 95% CI 0·99–1·20; p=0·092). In patients admitted to hospital with COVID-19, lopinavir–ritonavir was not associated with reductions in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death.

Other candidates targeting Mpro

Zhang (manuscript on bioRxiv: https://www.biorxiv.org/content/10.1101/2020.02.17.952879v1) determined the crystal structure of the unliganded Mpro at 1.75 A resolution and used this structure to guide optimization of a series of **alpha-ketoamide inhibitors**. The main goal of the optimization efforts was improvement of the pharmacokinetic properties of the compounds.

Numerous *in silico* studies aimed at finding Mpro/3CLpro inhibitors. For instance, based on the synergy of virtual screening, docking and molecular dynamics techniques, Macchiagodena (on arXiv: https://arxiv.org/abs/2002.09937) identified lead compounds for the non-covalent inhibition of Mpro of SARS-CoV-2. Ligands were found to share a common binding pattern with aromatic moieties connected by rotatable bonds in a pseudo-linear arrangement. Molecular dynamics calculations confirmed the stability in the Mpro binding pocket of most potent binder identified by docking, namely a **chlorophenyl-pyridyl-carboxamide derivative.**

Ton (Mol Inf 2020, see ***below***) developed a novel deep learning platform - Deep Docking (DD) which provides fast prediction of docking scores of Glide (or any other docking program) and, hence, enables structure-based virtual screening of billions of purchasable molecules in a short time. The authors applied DD to all 1.3 billion compounds from ZINC15 library to identify top 1000 potential ligands for SARS-CoV-2 Mpro protein.

Various authors, such as Kandeel (Life Sci 2020, see ***below***), focused on screening FDA-approved drugs. Using this approach, ribavirin, anti-hepatitis B virus (telbivudine), two vitamins (vitamin B12 and nicotinamide) and other miscellaneous systemically acting drugs were identified as potential blockers of SARS-CoV-2 Mpro. In another example, Jin (Nature 2020, see ***below***) assayed over 10 000 compounds including approved drugs, drug candidates in clinical trials, and other pharmacologically active compounds as inhibitors of Mpro. Six of these compounds inhibited Mpro with IC50 values ranging from 0.67 to 21.4 μM. **Ebselen** also exhibited promising antiviral activity in cell-based assays.

To the best of our knowledge, the *in vitro*, *in vivo*, and toxicological evaluations of the compounds that have been identified by such *in silico* work has not been documented yet.

Danoprevir

A study described by Zhang, Wang, Tu et al (J Med Vir 2020, see ***below***) enrolled 33 COVID-19 patients in Nanchang from 27th January to 24th February 2020. Patients were divided into two groups according to different treatment plans (danoprevir and lopinavir/ritonavir). COVID-19 patients treated with danoprevir or lopinavir/ritonavir were all improved and discharged. Additionally, the authors found that the mean time to achieve both negative nucleic acid testing and hospital stays of patients treated with danoprevir were significantly shorter than those of patients with lopinavir/ritonavir.

Other drug candidates

Nitazoxanide

Nitazoxanide, a commercial antiprotozoal agent with antiviral potential against a broad range of viruses including human and animal coronaviruses, inhibited infection of Vero E6 cells by a clinical isolate of SARS-CoV-2 at a low-micromolar concentration (EC50 = 2.12 μM; CC50 > 35.53 μM; SI > 16.76). Further *in vivo* evaluation of this drug against SARS-CoV-2 infection was recommended by Wang (Cell Res 2020, see ***below***).

Ivermectin

As the epidemic continues to progress, more and more compounds are described as potential therapeutics with antiviral activity against SARS-CoV-2. For instance, ivermectin (Caly Antivir Res 2020, see ***below***), a widely-approved anti-parasitic previously shown to have broad-spectrum anti-viral activity *in vitro*, has been found to inhibit SARS-CoV-2, with a single addition to Vero-hSLAM cells 2 hours post-infection with SARS-CoV-2 inducing a ~5000-fold reduction in viral RNA at 48 h. Of note, the much higher required dosage for the antiviral as compared to the antiparasitic effects of the drug seriously hampers the likelihood of further development of this compound against COVID-19. The concentration resulting in IC50 reported being 2 μM was > 35x higher than the maximum plasma concentration (Cmax) after oral administration of the approved dose of ivermectin when given in a fasting state (reviewed by Elkholy Cureus 2020, see ***below***) . Predicted lung IC50, when given the approved dose of ivermectin, was 0.0857 μM. Nevertheless, at doses 10x higher than the approved dose, the predicted lung IC50 was 0.817 which remains below the IC50 for effective inhibition of viral replication. Nevertheless, a retrospective analysis of 280 patients with confirmed COVID-19 infection found lower mortality in the ivermectin group (15%) compared to the control group (25.2%) (95% CI 0.29 - 0.96, P = .03). After adjustment for the mortality risks between both groups, the mortality benefit remained significant (hazard ratio (HR) 0.37, CI 0.19 - 0.71, p = .03). Elkholy (Cureus 2020, see ***below***) suggested that inhaled ivermectin should be evaluated as a potential broad-spectrum antiviral against respiratory viruses, including COVID-19.

Combination therapies

Numerous reports describe the use of combined drugs as potential COVID-19 therapies. On one hand, synergies have been identified *in vitro*, as exemplified by a combination of remdesivir and emetine (Choy Antivir Res 2020, see ***below***). The data suggested that such combinational therapy may help reduce the effective concentration of compounds below the therapeutic plasma concentrations and provide better clinical benefits.

Various drug combinations have also been evaluated (and are still under evaluation) in clinical studies. For instance, Hung (Lancet 2020, see ***below***) reported data from an open-label, randomised, phase 2 trial in 127 adults with COVID-19 that evaluated a combination of **lopinavir/ritonavir with ribavirin and interferon β**. The trial compared a 14-day combination of lopinavir 400 mg and ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million international units of interferon β-1b on alternate days (combination group) or to 14 days of lopinavir 400 mg and ritonavir 100 mg every 12 h (control group). 86 were randomly assigned to the combination group and 41 were assigned to the control group. The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [8–15]; hazard ratio 4·37 [95% CI 1·86–10·24], p=0·0010). Adverse events included self-limited nausea and diarrhoea with no difference between the two groups. No patients died during the study.

In another example, Chen (manuscript on medRxiv: https://www.medrxiv.org/content/10.1101/2020.03.22.20034041v1) reported on the first clinical study using danoprevir (Ganovo®), an HCV protease inhibitor marketed in China since 2018, combined with ritonavir (NCT04291729), in the presence or absence of α-interferon nebulization. The data from this small study suggested that the combination is well tolerated by COVID-19 patients (moderate cases included). After 4 to 12-day treatment, all eleven patients enrolled were discharged from the hospital.

Comparative clinical trials

A number of small size clinical trials evaluated more than one therapeutic candidate against COVID-19. Shi (J Med Vir 2020, see ***below***), for instance, reported on a small randomized clinical trial in 184 patients in Shangai, who received various treatments. They were divided into 7 groups: the symptomatic treatment group (n=17), arbidol group, lopinavir/ritonavir group, arbidol+lopinavir/ritonavir group, interferon group, interferon+lopinavir/ritonavir group, and interferon+darunavir group. Treatment duration was 5 days. No significant differences were found among the groups in terms of the proportion of patients with pneumonia resolution (P=0.151) after treatment or the length of hospital stay (P=0.116).

However, various statistically well-powered studies have also been reported. Solidarity is an international clinical trial to help find an effective treatment for COVID-19, launched by the WHO and partners. It is one of the largest international randomized trials for COVID-19 treatments, enrolling almost 12 000 patients in 500 hospital sites in over 30 countries (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments). As reported by WHO on October 15 2020, interim results from the Solidarity Therapeutics Trial showed that remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon regimens appeared to have little or no effect on 28-day mortality or the in-hospital course of COVID-19 among hospitalized patients (https://www.who.int/news/item/15-10-2020-solidarity-therapeutics-trial-produces-conclusive-evidence-on-the-effectiveness-of-repurposed-drugs-for-covid-19-in-record-time).

As an add-on trial of the Solidarity consortium of trials, DisCoVeRy is a phase III, open-label, adaptive, controlled, multicentre clinical trial in which hospitalised patients with COVID-19 in need of oxygen therapy are randomised between five arms: (1) a control group managed with standard of care and four therapeutic arms with re-purposed antiviral agents: (2) remdesivir + standard of care, (3) lopinavir/ritonavir + standard of care, (4) lopinavir/ritonavir

associated with interferon (IFN)-β-1a + standard of care and (5) hydroxychloroquine + standard of care (Ader BMJ Open 2020, see ***below***).

In the UK, the Recovery trial is testing candidate treatments including low-dose dexamethasone (now only recruiting children); azithromycin; tocilizumab; convalescent plasma; REGN-COV2 and aspirin (https://www.recoverytrial.net/)

Biological response modifiers

Biological response modifiers (BRM) are substances that interact with and modify the host immune system by acting on a therapeutic target considered important in the pathogenic process of the disease (Lacoma Front Imm 2019, see ***below***). They are now established as therapies for malignancies, transplant rejection, as well as several immune disorders, and can also provide protection against infectious diseases. They include immunostimulatory agents capable of enhancing host defence mechanisms, as well as compounds offering protection against the negative consequences of immune responses. They include antimicrobial peptides, therapeutic small molecules, therapeutic antibodies, cytokines and other immumodulators. Controlling cytokine production and inflammatory response appears as a desirable objective, given that they are responsible for the accumulation of cells and fluids. However, as pointed out by Li, Fan et al. (J Med Virol 2020, see ***below***), this strategy remains challenging as long as immune response parameters that can be inhibited specifically without compromising the beneficial host defence have not been identified. For instance, completely blocking a proximal event in the immune response (e.g., activation of interferon response-related pattern recognition receptors) seems unwise considering its general role in regulating host defence.

Interferon-α

During the SARS outbreak in 2003, an animal study revealed that recombinant human IFN-α2b spray can prevent SARS CoV infection in Rhesus monkey model by inhibiting virus infection and replication (Shen World J Pediatr 2020, see ***below***). Further clinical evaluation revealed that recombinant human IFN-α2b spray can effectively reduce the infection rate of respiratory syncytial virus, influenza virus, adenovirus and SARS-CoV. The "Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Standards (fourth edition) and Diagnosis, treatment and prevention of 2019 novel coronavirus infection in children: experts' consensus statement" of the National Health Commission of People's Republic of China also listed IFN-α atomization as a treatment option for COVID-19 pneumonia. An ongoing clinical trial in China evaluates the **preventive** effect of recombinant human interferon-α nasal drops on SARS-CoV-2 infection in medical staff (NCT04320238, https://clinicaltrials.gov/ct2/show/NCT04320238?term=healthy+coronavirus&recrs=abdf&type=Intr&draw=2).

Anti-inflammatory therapies

Corticosteroids

Corticosteroids were widely used during the outbreaks of SARS and MERS CoVs and are being used in patients with COVID-19 in addition to other therapeutics. However, interim guidance from WHO issued on March 13 2020 (Clinical management of severe acute respiratory infection when novel coronavirus (COVID-19) infection is suspected: https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf) initially advised against the use of corticosteroids unless indicated for another reason. The same conclusion was reported by Russell (Lancet 2020, see ***below***) who concluded from a literature review that no unique reason exists to expect that patients with COVID-19 will benefit from corticosteroids, and that they might be more likely to be harmed with such treatment. A subsequent publication by Shang (Lancet 2020, see ***below***) noted that the existing evidence on this topic was inconclusive, and even systematic reviews and meta-analyses on this topic reached differing conclusions. The authors recommended short courses of corticosteroids at low-to-moderate dose, used prudently, for critically ill patients with COVID-19 pneumonia. A similar recommendation was made by Zhou (Signal Transduct Target Ther 2020, see ***below***).

Veronese (Front Med 2020, see ***below***) reviewed the use of corticosteroids in COVID-19 pneumonia. Four studies with 542 Chinese participants were included. The data did not fully support the routine use of corticosteroids in COVID-19, but some findings suggested that methylprednisolone could lower the mortality rate in more severe forms of the condition.

In a later review and meta-analysis, Lu (Ann Transl Med 2020, see ***below***) retrieved 23 studies, including one randomized controlled trial and 22 cohort studies, with a total of 13,815 patients. The authors concluded that glucocorticoid therapy reduced the duration of fever, but not mortality, duration of hospitalization or lung inflammation absorption. Long-term use of high-dose glucocorticoids increased the risk of adverse reactions such as coinfections.

However, breakthrough data were obtained from the Randomised Evaluation of COVID-19 therapy (RECOVERY) trial, a randomized, controlled, open-label, adaptive, platform trial comparing a range of possible treatments with usual care in patients hospitalized with COVID-19. Preliminary results of the study for the comparison of dexamethasone 6 mg given once daily for up to ten days vs. usual care alone are available (Recovery collaborative group NEJM 2020, see ***below***). The primary outcome was 28-day mortality. A total of 2104 patients was randomly allocated to receive dexamethasone and compared with 4321 patients concurrently allocated to usual care. Overall, 454 (21.6%) patients allocated dexamethasone and 1065 (24.6%) patients allocated usual care died within 28 days. The proportional and absolute mortality rate reductions varied significantly depending on level of respiratory support at randomization (test for trend p<0.001): dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p<0.001), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p=0.14).

Updated guidance on the use of corticosteroids for COVID-19 was provided by WHO on September 2nd 2020 (https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1).

Anti-IL-6 receptor

IL-6 may play a role in driving the overactive inflammatory response in the lungs of patients who are severely or critically ill with COVID-19. A single-arm study of **tocilizumab** (Actemra), a humanized recombinant monoclonal antibody directed against the IL-6 receptor, in 21 Chinese patients with severe pneumonia provided preliminary data supporting the role of IL-6 in COVID-19 (https://sfar.org/download/effective-treatment-of-severe-covid-19-patients-with-tocilizumab/). Another report by Luo (J Med Vir 2020, see ***below***) described a retrospective observational study of tocilizumab in 15 patients. Although treatment ameliorated the increased CRP in all patients rapidly, for the 4 critically ill patients who received only single dose of tocilizumab, 3 of them died and the CRP level in the last patient failed to return to normal range with a clinical outcome of disease aggravation. Serum IL-6 level tended to further spike first and then decreased after tocilizumab therapy in 10 patients. A persistent and dramatic increase of IL-6 was observed in the 4 patients with treatment failure.

Alzghari (J Clin Virol 2020, see ***below***) reviewed information available from 4 case reports in the U.S., Switzerland, France and China, and 2 retrospective studies in respectively 15 and 21 patients in China. The authors highlighted the parameters to be monitored upon tocilizumab therapy, and the unknowns of the safety profile.

Table 12 Comparison of Major Tocilizumab COVID-19 Studies Reported to Date (from Parr JAMA 2020)

Study characteristic	Gupta et al[3] (STOP-COVID)	Salvarani et al[1] (RCT-TCZ-COVID-19)	Hermine et al[2] (CORIMUNO-TOCI-1)	COVACTA[12]	EMPACTA[13]
Design					
Type	Observational retrospective	Randomized prospective	Randomized prospective	Randomized prospective	Randomized prospective
Blinded	NA	No	No	Yes (double)	Yes (double)
Placebo-controlled	NA	No	No	Yes	Yes
Enrollment					
No. of sites	68	24	9	67	69
Countries	US	Italy	France	Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, United Kingdom, US	Brazil, Kenya, Mexico, Peru, South Africa, US
No. of participants	3924	126	131	450	389
No. tocilizumab treated	433	60[a]	63	225[b]	194[b]
Clinical severity[c]					
Moderate	No	No	No	No	No
Severe	Yes	Yes	Yes	Yes	Yes
Critical	Yes	No	No	Yes	No
Intervention					
Tocilizumab	Within 2 d of ICU admission	8 mg/kg ×2 Doses, 12 h apart	8 mg/kg ×1, Possible second dose on day 3	8 mg/kg ×1, Possible second dose	8 mg/kg ×1, Possible second dose
Comparator	Usual care	Usual care	Usual care	Usual care plus placebo	Usual care plus placebo
Outcomes[d]					
Primary, effect size	Time to death: Threshold for efficacy met; HR, 0.71 (95% CI, 0.56 to 0.92) 30-d mortality: Threshold for efficacy met; RD, 9.6% (95% CI, 3.1% to 16.0%)	Pao_2:Fio_2 <150 mm Hg, ICU admission, or death: Threshold for efficacy not met; RR, 1.05 (95% CI, 0.59 to 1.86)[e]	WHO-CPS score >5 on day 4: Threshold for efficacy not met; ARD, −9.0% (90% CrI, −21.0% to 3.1%); posterior probability of ARD <0 of 89.0% Survival without NIV or MV by day 14: Threshold for efficacy met; HR, 0.58 (90% CrI, 0.33 to 1.00), posterior probability of HR<1 of 95.0%	Difference in clinical status using a 7-category scale at day 28: Threshold for efficacy not met; OR, 1.19 (95% CI, 0.81 to 1.76)	Death or MV by day 28: Threshold for efficacy met; HR, 0.56 (95% CI, 0.32 to 0.97)
28- or 30-d mortality, tocilizumab vs comparator, effect size[f]	27.5% vs 37.1%; RD, 9.6% (95% CI, 3.1% to 16.0%)	3.3% vs 1.6%; RR, 2.10 (95% CI, 0.20 to 22.6)	11.1% vs 11.9%; aHR, 0.92 (95% CI, 0.33 to 2.53)	19.7% vs 19.4%; ARD, 0.3% (95% CI, −7.6% to 8.2%)	10.4% vs 8.6%; ARD, 2.0% (95% CI, −5.2% to 7.8%)
Trial registration	NCT04343898	NCT04346355	NCT04331808	NCT04320615	NCT04372186

Abbreviations: aHR, adjusted hazard ratio (HR); ARD, median absolute risk difference; CORIMUNO-TOCI-1, Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients-Tocilizumab Trial; CrI, credible interval; ICU, intensive care unit; MV, mechanical ventilation; NA, not applicable; NIV, noninvasive ventilation; OR, odds ratio; RCT-TCZ-COVID-19, Open-label Randomized Multicenter Study to Evaluate the Efficacy of Early Administration of Tocilizumab in Patients With COVID-19 (coronavirus disease 2019) Pneumonia; Pao_2:Fio_2, ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen; RD, risk difference; RR, rate ratio; STOP-COVID, Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19; WHO-CPS, WHO 10-point Clinical Progression Scale.

[a] Treatment assignment at enrollment. Crossover between treatment arms was permitted in the setting of clinical worsening.

[b] Numbers are derived from ClinicalTrials.gov and F Hoffman-La Roche Ltd.[12,13] Number of tocilizumab-treated participants is assumed based on planned 1:1 tocilizumab to placebo assignment.

[c] Definitions varied by study. This classification attempts to group by National Institutes of Health COVID-19 management categories.[7] Patients were or were not included with a given NIH severity scale.

[d] Efficacy estimated by the STOP-COVID investigators using an emulated target trial with observational data.

[e] Stopped early by the data and safety monitoring board for futility.

[f] Not a primary outcome for all studies; included here to facilitate comparison.

Colaneri (Microorganisms 2020, see ***below***) reported the outcome of a small study, where 21 patients who received tocilizumab were matched to 21 patients who received a combination of hydroxychloroquine, azithromycin and prophylactic dose of low weight heparin. No adverse event was detected following tocilizumab administration. This study found that treatment with tocilizumab did not significantly affect ICU admission (OR 0.11; 95% CI between 0.00 and 3.38; p = 0.22) or 7-day mortality rate (OR 0.78; 95% CI between 0.06 and 9.34; p = 0.84) when compared with the

drug combination. However, in view of the small sample size, this study did not seem to be adequately powered to demonstrate differences in efficacy.

A review by Khiali (J Clin Pharmacol 2020, see ***below***) discussed available evidence regarding the potential therapeutic role of tocilizumab and important clinical issues in the treatment of ARDS related to COVID-19. However, randomized trials data were released subsequently, which suggested a potential role for tocilizumab in COVID-19 while not showing clear evidence of efficacy (Parr JAMA 2020, see ***below***). In contrast to findings from STOP-COVID and a growing number of observational studies indeed, none of the tocilizumab randomized trials reported mortality benefit at 28 or 30 days, and only 2 of these reported outcomes meeting predefined thresholds for clinical efficacy (***Table 12*** above). Double-blinded, randomized, controlled trials of longer-term outcomes remain necessary to ascertain whether tocilizumab can reduce the severity of illness and the death rate without higher rates of treatment-related adverse events and secondary infections. At least 5 other randomized controlled trials of tocilizumab in COVID-19 have been reported (NCT04335071; NCT04356937; NCT04381936; NCT04363736; NCT04409262).

As reported by Tleyjeh (Clin Microbiol Infect 2020, see ***below***) up to now, randomized controlled trials did not show that tocilizumab reduces short-term mortality, but low certainty evidence from cohort studies suggests an association between tocilizumab and lower mortality. The authors did not observe a higher risk of infections or adverse events with tocilizumab use. This living review will continuously evaluate the role of tocilizumab in COVID-19 treatment.

Sarilumab (Kevzara) is a fully-human monoclonal antibody that inhibits the IL-6 pathway by binding and blocking the IL-6 receptor. An adaptive phase 2/3, randomized, double-blind, placebo-controlled study assessing the efficacy and safety of Sarilumab for hospitalized patients with COVID-19 has been conducted in the U.S. (NCT04315298; 1912 participants). At the time of writing, only preliminary data from the trial have been disclosed (https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-27-12-58-00). Additional randomized controlled trials have been reported in other countries (e.g. NCT04322773 in Denmark; NCT04357808 in Spain).

JAK-STAT inhibitors

Baricitinib is a powerful anti-inflammatory that, as a JAK-STAT signalling inhibitor, is likely to be effective against the consequences of the elevated levels of cytokines observed in people with severe COVID-19. Richardson (Lancet Inf Dis 2020, see ***below***) further acknowledged that that using a JAK1 and JAK2 inhibitor to treat a viral disease might appear illogical given that the antiviral effects of interferons are largely mediated by the JAK–STAT signalling pathway. However, the authors do not recommend that baricitinib or other JAK inhibitors be given to individuals at an early stage of infection. Clinical trials assessing the efficacy of baricitinib to treat COVID-19 are ongoing (NCT04321993) or planned (NCT04320277).

In a pilot uncontrolled trial, baricitinib at 4 mg/day/orally (combined with lopinavir-ritonavir) was given to 12 pneumonia patients with moderate COVID-19 (Cantini J Infect 2020, see ***below***). No adverse events were recorded, after 2 weeks in treated patients. Clinical and respiratory parameters significantly improved at 2 weeks. None of the baricitinib-treated patients required admission to ICU.

Ruxolitinib, a JAK1/2 inhibitor, has also been assessed in COVID-19 patients. Cao reported a prospective, multicenter, single-blind, randomized controlled phase II trial involving patients with severe disease (J Allergy Clin Immunol 2020, see ***below***). Treatment with ruxolitinib plus standard-of-care was not associated with significantly accelerated clinical improvement in patients with severe coronavirus disease, although ruxolitinib recipients had a numerically faster clinical improvement.

Complement inhibitors

The manifestations of severe COVID-19 such as the ARDS, sepsis and multiorgan failure have an established relationship with activation of the complement cascade. Polycarpou (EMBO Mol Med 2020, see ***below***) collected

evidence linking severe COVID-19 disease directly with dysfunction of the complement pathways. This information lended support for a therapeutic anti-inflammatory strategy against complement, where a number of clinically ready potential therapeutic agents are available.

Preliminary data obtained with anti-complement **C5** therapy with eculizumab in 4 COVID-19 patients were reported by Diurno (Eur Rev Med Pharmacol Sci 2020, see ***below***). While positive results were obtained, interpretation is complicated by the fact that patients received not only eculizumab, but also anticoagulant therapy with Enoxaparin 4000 IU/day via subcutaneous injection, antiviral therapy with Lopinavir 800 mg/day + Ritonavir 200 mg/day, hydroxychloroquine 400 mg/day, ceftriaxone 2 g/day IV, and vitamine C 6 g/day for 4 days.

Mastaglio (Clin Imm 2020, see ***below***) reported the clinical course of a patient with severe ARDS due to COVID-19 pneumonia who was successfully treated with the compstatin-based complement **C3** inhibitor AMY-101. C3 interception with compstatin-based inhibitors (such as AMY-101) may offer broader therapeutic coverage than anti-C5 or anti-C5a agents by blocking simultaneously generation of all downstream proinflammatory mediators involved in SARS-CoV-2-induced ARDS and thrombotic microangiopathies.

Immune checkpoint inhibitors

Immune checkpoint inhibitors are being considered for their potential to augment the host response in sepsis. PD-1 and PD-L1 are indeed key mediators in T cell depletion in sepsis patients. Animal models have shown that blocking PD-1 or PD-L1 can prevent T cell death, regulate cytokine production, reduce organ dysfunction and reduce death in sepsis. Previous experience showed the clinical safety of anti-PD-1 antibody in sepsis patients through randomized, placebo-controlled trials. A phase 2 clinical trial is reported as planned among 120 COVID-19 patients to evaluate anti-PD-1 antibody treatment vs. thymosin vs. control (NCT04268537, https://clinicaltrials.gov/ct2/show/NCT04268537?term=anti-PD-1&cond=COVID-19&draw=2&rank=1).

BTK inhibitors

Based on observations in 5 patients on ibrutinib, Treon (Blood 2020, see ***below***) suggested that ibrutinib and possibly other BTK-inhibitors may provide protection against lung injury, and even improve pulmonary function in hypoxic patients with COVID-19.

Renin–Angiotensin–Aldosterone System inhibitors

Placebo-controlled clinical trials of **losartan**, an angiotensin-receptor blocker, as a treatment for COVID-19 are being conducted among patients who have not previously received treatment with a Renin–Angiotensin–Aldosterone System inhibitor and are either hospitalized (NCT04312009) or not hospitalized (NCT04311177) (Vaduganathan NEJM 2020, see ***below***).

Other therapeutic antibodies

Several other antibodies specific for host targets that are developed in the context of lung disease might appear as promising for COVID-19 therapy. Some antibodies may indeed have the potential to reduce prolonged damaging cellular infiltration during severe lung infections (Elbahesh Front Imm 2019, see ***below***). For instance, angiopoietin-like 4 (ANGPTL4) is a soluble angiogenic regulating protein. Following proteolytic cleavage, the C-terminal portion (cANGPTL4) is involved in integrin-dependent wound repair and can regulate vascular permeability. ANGPTL4 is significantly elevated in lung biopsies from influenza virus-induced pneumonia patients. In mouse studies, neutralizing anti-ANGPTL4 antibodies reduced pulmonary tissue leakiness, significantly accelerating lung recovery. Vascular leakage is a hallmark of many infectious diseases, including those caused by SARS and MERS CoVs (Li Oncotarget 2015, see ***below***). The roles of ANGPTL4 in SARS-CoV-2 infection is still unclear, but warrant future investigations.

Antimicrobial peptides

Antimicrobial peptides (AMPs), also termed host defence peptides, can be produced as part of the host's innate immune system during an infection process (Cardoso Int J Mol Sci 2019, see ***below***; Brice Curr Med Chem 2019, see ***below***). These peptides belong to a broad group of molecules produced by many tissues and cell types in a variety of organisms, including plants, invertebrates, vertebrates, fungi and bacteria. The majority of AMPs are composed of relatively small (<10 kDa), cationic and amphipathic molecules, mostly consisting of 6 to 50 amino acid residues. The different amino acid compositions lead to structural properties in terms of amphipathicity, net positive charge, shape and size, which favour interaction with microbial surfaces, insertion into lipid bilayers and induction of membrane damage. It is therefore not surprising that human AMPs display activity against enveloped viruses as well as bacteria and fungi (Brice Curr Med Chem 2019, see ***below***). However, these peptides also exhibit activity against a wide range of non-enveloped viruses, acting at a number of different steps in viral infection. Recent studies have begun to elucidate the antiviral properties of AMPs as well as their role in regulation of inflammation and chemoattraction. AMPs have been suggested as promising therapies against viral pathogens (Ahmed Viruses 2019, see ***below***), even though experimental data are still needed to support this proposal.

The antiviral activity of **defensins**, a class of AMPSs, was first reported in 1986. Since then, defensins have demonstrated *in vitro* effects against HIV, influenza A virus, human adenovirus, human papillomavirus, RSV, herpes simplex virus and SARS-CoV. However, few studies in animal models of virus infection have been reported. A murine β-defensin 1-deficient mouse model showed that MBD1, the murine counterpart of HBD1, participated in the protection of mice from influenza infection via a mechanism other than the inhibition of viral replication (Park 2018). Innovation Pharmaceuticals has announced the consideration of its defensin mimetic drug candidate **Brilacidin** for the potential treatment of Covid-19, the disease caused by the coronavirus (https://www.pharmaceutical-technology.com/news/innovation-pharmaceuticals-covid-19-drug/). Brilacidin is a small molecule in late-phase development. The drug is said to have shown antibacterial, anti-inflammatory and immunomodulatory activity in different clinical studies.

Cell-based therapies

A rapidly increasing number of clinical investigations of cell-based therapy approaches for COVID-19 is reported. These utilise a range of different cell sources, doses, dosing strategies, and targeted patient populations. To provide a rational strategy to maximise potential therapeutic use, Khoury (Eur Respir J 2020, see ***below***) recommended a good understanding of the relevant pre-clinical studies and postulated mechanisms of actions in respiratory virus-induced lung injuries.

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) have been widely used in cell-based therapy, from basic research to clinical trials. Safety and effectiveness have been clearly documented in many clinical trials, especially in the immune-mediated inflammatory diseases, such as graft versus-host disease and systemic lupus erythematosus. MSCs play a positive role mainly in two ways, namely immunomodulatory effects and differentiation abilities. MSCs can secrete many types of cytokines by paracrine secretion or make direct interactions with immune cells, leading to immunomodulation. The immunomodulatory effects of MSCs are triggered further by the activation of TLR receptor in MSCs, which is stimulated by pathogen-associated molecules such as LPS or double-stranded RNA. Several review papers provide a rationale to the use of such therapy in COVID-19 patients (see for instance Yao J Int Med Res 2020, see ***below***).

In a pilot study (ChiCTR2000029990), MSCs transplantation could cure or improve the functional outcomes of seven patients without observed adverse effects (Leng Aging Dis 2020, see ***below***). The pulmonary function and symptoms of these patients were significantly improved in 2 days after MSC transplantation. Among them, two common and one severe patient were recovered and discharged in 10 days after treatment. After treatment, the peripheral lymphocytes were increased, the CRP decreased, and the overactivated cytokine-secreting immune cells CXCR3+CD4+ T cells,

CXCR3+CD8+ T cells, and CXCR3+ NK cells disappeared in 3-6 days. In addition, a group of CD14+CD11c+CD11bmid regulatory DC cell population dramatically increased. Meanwhile, the level of TNF-α was significantly decreased, while IL-10 increased in MSC treatment group compared to the placebo control group. Furthermore, the gene expression profile showed MSCs were ACE2- and TMPRSS2- which indicated MSCs are free from COVID-19 infection. Several larger trials of this therapy are currently either ongoing or planned in China and other countries (Brazil, Jordan, France).

Cardiosphere-derived cells

Cardiosphere-derived cells (CDCs) are stromal/progenitor cells, derived from heart tissue, with a distinctive antigenic profile (CD105+, CD45−, CD90low). Since CDCs were first isolated from human endomyocardial biopsies in 2007, these cells have been tested in > 200 patients in clinical trials for myocardial infarction, heart failure with reduced and preserved ejection fraction, Duchenne muscular dystrophy, pulmonary arterial hypertension, and hypoplastic left heart syndrome. These trials, along with extensive preclinical investigation (~ 200 publications from > 55 independent laboratories worldwide), have demonstrated immunomodulatory and anti-inflammatory effects of CDCs. Head-to-head comparisons in preclinical models indicate that CDCs may be more effective than MSCs with regards to paracrine factor secretion and myocardial remodeling. Given the safety record of CDCs in humans, and the substantial body of evidence confirming relevant disease-modifying bioactivity, applicability to COVID-19 seemed compelling, particularly in the hyperinflammatory stage of the illness. Singh (Basic Res Cardiol 2020, see ***below***) evaluated safety and impact of administration of allogeneic CDCs, formulated for intravenous infusion as CAP-1002, in 6 critically ill COVID-19 patients. No patient experienced any complications related to CAP-1002 administration. Patients 1 and 4 received a second dose of CAP-1002, after pre-treatment with diphenhydramine, likewise with no complications. All intubated patients improved clinically after cell infusion, except patients 4 and 6, who are still in ICU but remain stable.

High-Dose Intravenous Immunoglobulin

Cao (Open Forum Infect Dis 2020, see ***below***) reported on the use of high-dose Intravenous Immunoglobulin at 0.3–0.5 g per kg weight per day for five days in 3 patients with deteriorating condition. None of the 3 patients reported any adverse events. All patients were clinically improved shortly after the administration, with their temperature back to normal in 1-2 days and breathing difficulties alleviating in 3-5 days. Confounding factors did exist, including the use of different antivirals in 2 of the 3 patients at various time points and a short course of steroids in patient 3.

Antibodies

Polyclonal antibodies

Convalescent plasma

The effectiveness of convalescent plasma for the treatment of SARS, as reviewed by Mair-Jenkins (J Infect Dis 2015, see ***below***), was assessed by 8 studies reporting outcomes for 214 patients with SARS in total. The absolute reduction in the risk of mortality varied from 7% (95% CI, -2.39 to 18.68) to 23% (95% CI, 5.59–42.02) in 2 studies at medium to high risk of bias. Subgroup analyses suggested that early treatment was beneficial. Four non-comparative studies found that the case-fatality rate varied from 0% (0/1) to 12.5% (10/80) in treated subjects. Increased antibody levels were detected up to day 5 after treatment in 1 study of HCWs (which was at high risk of bias). Experience with convalescent plasma infusion has also been obtained in the context of MERS-CoV infections. Ko (Antivir Ther 2018, see ***below***), based on experience with 3 patients, suggested that for effective convalescent plasma infusion against MERS, donor plasma with a neutralization activity (PRNT titre) ≥1:80 should be used. However, the observation that convalescent plasma infusion led to possible transfusion-related acute lung injury (TRALI) in a MERS patient in Korea suggests that convalescent plasma therapy should be cautiously approached (Chun Ann Lab Med 2016, see ***below***).

Zhang and Liu (J Med Vir 2020, see ***below***) identified this approach as a potential treatment for COVID-19. Information released in the media soon indicated that the procedure was evaluated clinically in China

(https://www.scoop.it/topic/virusworld/p/4115315422/2020/02/14/china-seeks-plasma-from-recovered-patients-to-treat-virus). A plasma donation program had been launched in Zhejiang Province (http://www.xinhuanet.com/english/2020-02/19/c_138799179.htm). The plasma donated by recovered coronavirus patients was said to be used for treatment of COVID-19 patients in critical condition.

Shen (JAMA 2020, see ***below***) reported 5 critically ill patients with laboratory-confirmed COVID-19 and ARDS who received convalescent plasma with a SARS-CoV-2–specific antibody (IgG) binding titer greater than 1:1000 and a neutralization titer greater than 40 (obtained from patients who recovered from COVID-19). Following plasma transfusion, viral loads decreased and became negative within 12 days after the transfusion, and SARS-CoV-2-specific ELISA and neutralizing antibody titers increased. ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital, and 2 are in stable condition at 37 days after transfusion. The small sample size of the study precludes conclusions in terms of effectiveness, but data from clinical trials are expected in a near future.

Another pilot study on convalescent plasma therapy (single 200 mL dose with neutralization activity greater than 1:640) in severe COVID-19 patients was reported by Duan (PNAS 2020, see ***below***). Data showed no severe adverse events and undetectable viral load after transfusion in 7/10 patients. Ye (J Med Vir 2020, see ***below***) reported a positive outcome in 6 patients treated with convalescent plasma. Ahn (J Kor Med Sci 2020, see ***below***) reported on 2 additional cases treated with convalescent plasma in Korea with positive outcome.

Liu (Nat Med 2020, see ***below***) reported the outcomes of thirty-nine hospitalized patients with severe to life-threatening COVID-19 who received convalescent plasma transfusion, and compared them against a cohort of retrospectively matched controls. These analyses suggested that convalescent plasma recipients were more likely than control patients to remain the same or have improvements in their supplemental oxygen requirements by post-transfusion day 14, with an odds ratio of 0.86 (95% CI: 0.75~0.98; p=0.028). Plasma recipients also demonstrated improved survival, compared to control patients (log-rank test: p=0.039). In a covariates-adjusted Cox model, convalescent plasma transfusion improved survival for non-intubated patients (hazard ratio 0.19 (95% CI: 0.05 ~0.72); p=0.015), but not for intubated patients (1.24 (0.33~4.67); p=0.752).

A position paper by Accorsi (Transfus Apher Sci 2020, see ***below***) gave recommendations on biological characteristics of a plasma preparation from convalescent donors. The authors support the evaluation of this therapeutic approach in more rigorous investigations.

Multiple randomized controlled clinical trials are ongoing to assess the efficacy and safety of anti-SARS-CoV-2 convalescent plasma (as reported for instance by Kumar Am J Emerg Med 2020, see ***below***; or NCT04390503, NCT04429854, NCT04366245, NCT04411667, NCT04442191, NCT04373460, NCT04390503, NCT04374526, NCT04323800). Some of these trials are reported as completed (e.g. NCT04442958, NCT04346446). However, to the best of our knowledge, the outcome of these studies has not been disclosed yet. One report described a trial conducted in China in a total of 103 participants with either severe or life-threatening laboratory-confirmed COVID-19 (ChiCTR2000029757). In this trial, use of convalescent plasma was not associated with a statistically significant improvement in time to clinical improvement within 28 days (Li JAMA 2020, see ***below***). Daniele (Int J Inf Dis 2020, see ***below***) identified the reports of 4 additional randomized controlled studies which have led to inconclusive or negative results, potentially due to lack of neutralizing antibody titer assessment in donated units and/or late treatment. More encouraging findings have been reported from retrospective or prospective propensity-score-matched studies in the USA. For instance, a preprint paper, published on medRxiv on 12 August, examined whether plasma reduced mortality, and included 35 322 patients who received transfusions between 4 April and 4 July at one of the 2807 participating US centres (https://www.medrxiv.org/content/10.1101/2020.08.12.20169359v1). The study, not peer-reviewed, said, “Earlier use of convalescent plasma was associated with lower observed rates of 7-day and 30-day mortality. The use

of convalescent plasma with higher antibody levels was associated with reduced 7-day and 30-day mortality." Experts have warned that although these early findings show promise there is not enough evidence to show that it works.

The US Food and Drug Administration authorized convalescent plasma for treating severe or life-threatening COVID-19 under individual-patient emergency Investigational New Drug applications in March 2020 (Tanne BMJ 2020, see ***below***; Mahase BMJ 2020, see ***below***). On 23 August, convalescent plasma was approved by the FDA for emergency use (EUA) in hospital patients with COVID-19. The announcement said they had concluded that plasma from recovered patients "may be effective" in treating the virus and that the "potential benefits of the product outweigh the known and potential risks." The move came despite the absence of results from randomised controlled trials. The data that were available to support EUA issuance were reviewed by Pau (Ann Int Med 2020, see ***below***).

Purified immune globulins

SAB-301 is a fully-human polyclonal IgG immunoglobulin (SAB-301) produced from hyperimmune plasma of transchromosomic cattle immunized with purified MERS-CoV spike protein nanoparticles vaccine (Beigel Lancet Inf Dis 2018, see ***below***). In a phase 1 trial, single infusions of SAB-301 up to 50 mg/kg appear to be safe and well-tolerated in healthy participants. However, no published data suggest that SAB-301 purified immune globulin is able to neutralize SARS-CoV-2. On March 6 2020, Takeda announced the development of an anti-SARS-CoV-2 polyclonal hyperimmune globulin, **TAK-888**, to treat high-risk individuals with COVID-19 (https://www.takeda.com/newsroom/featured-topics/rajeev-venkayya-president-global-vaccine-business-unit-on-the-latest-on-the-coronavirus-and-takeda/).

Monoclonal antibodies

The SARS-CoV and MERS-CoV neutralizing monoclonal antibodies (mAbs) and nanobodies with protective efficacy are specific to the S1 subunit of S protein, particularly the receptor-binding domain (RBD) (Jiang Em Micr Inf 2020, see ***below***). A range of mAbs were listed by WHO on January 24 2020 as potential candidates against COVID-19 (https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-RDBlueprint%28nCoV%29-2020.1-eng.pdf?ua=1), even though their ability to neutralize SARS-CoV-2 had not been confirmed. However, efforts soon shifted to the development of SARS-CoV-2-specific mAbs.

Lei (Nat Comm 2020, see ***below***) generated 2 fusion proteins, a first one obtained by connecting the extracellular domain of human ACE2 to the Fc region of the human immunoglobulin IgG1 and a second one containing an ACE2 mutant with low catalytic activity. These fusion proteins neutralized virus pseudotyped with SARS-CoV or SARS-CoV-2 S proteins *in vitro*. Miersch (manuscript on bioRxiv : https://doi.org/10.1101/2020.06.05.137349) described a panel of synthetic monoclonal antibodies, built on a human framework, that bind SARS-CoV-2 S protein, compete for binding with ACE2, and potently inhibit infection by SARS-CoV-2. These antibodies were found to have a range of neutralization potencies against live virus infection in Vero E6 cells, potently inhibiting authentic SARS-CoV-2 virus at sub-nanomolar concentrations.

Chen (Cell Mol Immunol 2020, see ***below***) reported the cloning of two human blocking mAbs using SARS-CoV-2 RBD-specific memory B cells isolated from recovered COVID-19 patients. These two mAbs can specifically bind to SARS-CoV-2 RBD, block the interaction between SARS-CoV- 2 RBD and hACE2 receptor, and lead to efficient neutralization of SARS-CoV-2 S protein pseudotyped virus infection. Wang (Nat Commun 2020, see ***below***) also described a human monoclonal antibody that neutralizes SARS-CoV-2: 47D11 binds a conserved epitope on the S RBD explaining its ability to cross-neutralize SARS-CoV and SARS-CoV-2, using a mechanism that is independent of receptor-binding inhibition. Subsequently, Ju (Nature 2020, see ***below***) reported the isolation and characterization of 206 RBD-specific monoclonal antibodies derived from single B cells from 8 individuals infected with SARS-CoV-2. The authors identified antibodies that potently neutralize SARS-CoV-2; this activity correlated with competition with ACE2 for binding to RBD.

Wrapp (Cell 2020, see ***below***) isolated single-domain antibodies (VHHs) from a llama immunized with prefusion-stabilized coronavirus spikes and neutralizing MERS-CoV or SARS-CoV-1 S pseudotyped viruses, respectively. The authors also showed cross-reactivity between the SARS-CoV-1 S-directed VHH and SARS-CoV-2 S and demonstrated that this cross-reactive VHH neutralizes SARS-CoV-2 S pseudotyped viruses as a bivalent human IgG Fc-fusion. Similarly, Dong (Em Micr Inf 2020, see ***below***) reported the design and evaluation of bi-specific llama VHH-Fc antibody. Data showed potent S/ACE2 blocking, with ~100% blocking at 36.7 nM, and ~95% blocking at 12.2 nM.

Of note, a review by Chenoweth (Immunol Cell Biol 2020, see ***below***) addressed the topic of the FcR and antibody engineering in the context of monoclonal antibody development against SARS-CoV-2. More recently, an overview of neutralizing monoclonal antibodies against SARS-CoV-2 has been made available by Yu (Sign Transd Target Ther 2020, see ***below***) (***Table 13***).

Table 13 Neutralizing monoclonal antibodies against SARS-CoV-2 (from Yu Sign Transd Target Ther 2020)

NMAbs's name	Type	Source	Preparation	Target	Assay and result
3F11	sdAb	Human	Humanized phage display library	RBD	PsV neutralization: IC_{50} – 3.8 ng/ml; LV neutralization: IC_{50} – 436 ng/ml.
BD-368-2	IgG	Human	B cells of convalescent patients; Single cell sequencing	RBD	PsV neutralization: IC_{50} – 1.2 ng/ml; LV neutralization: IC_{50} – 15 ng/ml; Full protection of mice: 20 mg/kg.
ab1	IgG	Human	Phage displayed Fab, scFv and VH libraries	RBD	Reporter Gene neutralization assay: 200 ng/ml; LV neutralization: ND_{100} < 400 ng/ml; Full protection of mice: 0.3 mg of IgG1 ab1.
CB6	IgG	Human	B cells of convalescent patients	RBD	PsV neutralization: ND_{50} – 0.036 μg/ml; LV neutralization: ND_{50} – 0.036 μg/ml; Protection of rhesus macaques: 50 mg/kg.
B38	IgG	Human	Peripheral blood of SARS-CoV-2-infected patients	RBD	LV neutralization: IC_{50} – 0.177 μg/ml; Protection of mice: Lung viral load reduced by 32.8% compared with PBS control.
H4	IgG	Human	Peripheral blood of SARS-CoV-2-infected patients	RBD	LV neutralization: IC_{50} – 0.896 μg/ml; Protection of mice: Lung viral load reduced by 26% compared with PBS control.
7B11 18F3	IgG	Mouse	Animal immunization; hybridoma technology	RBD	PsV neutralization: IC_{80} – 10 μg/ml. PsV neutralization: IC_{80} – 10 μg/ml.
P2C-1F11	IgG	Human	Plasma of convalescing patients	RBD	PsV neutralization: IC_{50} – 0.03 μg/ml.
rRBD-15	IgG	Human	A synthetic human Fab antibody library	RBD	PsV neutralization: IC_{50} – 12.2 nM.
VHH-72-Fc	HCAb	llama	Animal immunization and sequencing	RBD	PsV neutralization: IC_{50} ~ 0.2 μg/ml.
311mab-31B5 311mab-32D4	IgG	Human	B cells of convalescent patients	RBD	PsV neutralization: IC_{50} – 33.8 ng/ml. PsV neutralization: IC_{50} – 69.8 ng/ml.
CC12.1	IgG	Human	B cells of convalescent patients	RBD	PsV neutralization: IC_{50} – 0.019 μg/ml; LV neutralization: IC_{50} – 0.022 μg/ml; Full protection of Syrian hamsters: Antibody serum concentration of ~22 μg/ml.
COVA1-18 COVA2-15	IgG	Human	B cells of convalescent patients	RBD	PsV neutralization: IC_{50} – 8 ng/ml; LV neutralization: IC_{50} – 7 ng/ml. PsV neutralization: IC_{50} – 8 ng/ml; LV neutralization: IC_{50} – 9 ng/ml.
47D11	IgG	Chimeric antibody	Transgenic mice; hybridoma technology	RBD	PsV neutralization: IC_{50} – 0.061 μg/ml; LV neutralization: IC_{50} – 0.57 μg/ml.
S309	IgG	human	Peripheral blood of SARS-infected patients	RBD	PsV neutralization: IC_{50} – 3.5 nM; LV neutralization: IC_{50} – 79 ng/ml.
ADI-55689 ADI-55993 ADI-56000 ADI-55688 ADI-56046 ADI-56010 ADI-55690 ADI-55951	IgG	Human	Memory B cell repertoire of a convalescent SARS donor	RBD	PsV neutralization: IC_{50} – 0.05 ~ 1.4 μg/ml; LV neutralization: showed neutralizing activity at 100 nM.
REGN10989 REGN10987 REGN10933 REGN10934	IgG	Human	Transgenic mice; Peripheral blood of SARS-CoV-2-infected patients; Next Generation Sequencing	RBD	PsV neutralization: IC_{50} – 7.23 pM; LV neutralization: IC_{50} – 7.38 pM. PsV neutralization: IC_{50} – 40.6 pM; LV neutralization: IC_{50} – 42.1 pM. PsV neutralization: IC_{50} – 42.8 pM; LV neutralization: IC_{50} – 37.4 pM. PsV neutralization: IC_{50} – 54.4 pM; LV neutralization: IC_{50} – 28.3 pM.

H11-H4-Fc H11-D4-Fc	HCAb	llama	Phage display library	RBD	LV neutralization: ND_{50} – 6 nM. LV neutralization: ND_{50} – 18 nM.
H014	IgG	Chimeric antibody	Animal immunization and phage display	RBD	PsV neutralization: IC_{50} – 3 nM; LV neutralization: IC_{50} – 38 nM; Protection of mice: Lung viral load reduced by about 10 ~100 folds compared with PBS control.
COV2-2196 COV2-2130	IgG	Human	Peripheral blood of convalescent patients	RBD *	PsV neutralization: IC_{50} – 0.7 ng/ml; LV neutralization: IC_{50} – 15 ng/ml. PsV neutralization: IC_{50} – 1.6 ng/ml; LV neutralization: IC_{50} – 107 ng/ml.
2-15	IgG	Human	Peripheral blood of COVID-19 patients	RBD	PsV neutralization: IC_{50} – 0.7 ng/ml; LV neutralization: IC_{50} – 5 ng/ml; Protection of hamsters: Viral RNA copy numbers and infectious virus titers in lung tissues were reduced by 4 logs or more compared with PBS control.
CR3022	IgG	Human	Gene cloning; Protein expression	RBD	LV neutralization: IC_{50} – ~ 0.114 μg/ml.
4A8	IgG	Human	Peripheral blood of convalescent patients	NTD	PsV neutralization: EC_{50} – 49 μg/ml; LV neutralization: EC_{50} – 0.61 μg/ml.

SARS-CoV-2 monoclonal antibodies under clinical evaluation

Regeneron is developing REGN-COV2, an antibody cocktail of REGN10933 and REGN10987 being studied both for its prophylactic and therapeutic potential against SARS-CoV-2 (https://www.regeneron.com/covid19). Baum (Science 2020, see ***below***) evaluated the *in vivo* efficacy of this antibody cocktail in both rhesus macaques, which may model mild disease, and golden hamsters, which may model more severe disease. The authors demonstrated that REGN-COV-2 can greatly reduce virus load in lower and upper airways and decrease virus induced pathological sequelae when administered prophylactically or therapeutically in rhesus macaques. Similarly, administration in hamsters limited weight loss and decreased lung titers and evidence of pneumonia in the lungs. Clinical trials of REGN-COV2 began in mid-June. The clinical program involves four separate study populations: two for treatment and two for prevention of COVID-19. The first studies evaluated evaluating safety and efficacy in hospitalized and non-hospitalized patients with COVID-19 (NCT04425629, NCT04426695). A phase 3, randomized, double-blind, placebo-controlled study is currently ongoing to assess the efficacy and safety of the antibody cocktail in preventing SARS-CoV-2 infection in household contacts of individuals infected with SARS-CoV-2. The study is to enrol a total of 2000 volunteers (https://clinicaltrials.gov/ct2/show/NCT04452318).

Tychan develops TY027, a monoclonal antibody designed and engineered to SARS-CoV-2 by binding to a specific epitope of the S protein found on the surface of the virus (https://www.tychan.com/). A phase 1 first-in-Human, time lagged, randomised, placebo controlled, double blind, single ascending dose study of TY027 in healthy adult volunteers started on June 12 in Singapore (https://clinicaltrials.gov/ct2/show/NCT04429529?term=antibody&recrs=adefh&type=Intr&cond=COVID-19&draw=2&rank=29).

Monoclonal antibody LY-CoV555 is developed by Eli Lilly. LY-CoV555 is a potent, neutralizing IgG1 mAb directed against the S protein of SARS-CoV-2. LY-CoV555 emerged from a collaboration between Lilly and AbCellera. A randomized, double-blind, placebo-controlled, phase 2 study is ongoing to evaluate the efficacy and safety of LY3819253 in participants with mild to moderate COVID-19 Illness (https://clinicaltrials.gov/ct2/show/NCT04427501). On August 3, 2020, Eli Lilly announced the initiation of a Phase 3 trial studying LY-CoV555 for the prevention of SARS-CoV-2 infection and COVID-19 in residents and staff at long-term care facilities in the U.S. (skilled nursing facilities, commonly referred to as nursing homes, and assisted living facilities) (https://investor.lilly.com/news-releases/news-release-details/lilly-initiates-phase-3-trial-ly-cov555-prevention-covid-19-long).

STI-1499 is a monoclonal antibody developed by Sorrento Therapeutics. According to company news, the efficacy of the product has been demonstrated in a Syrian Hamster model of SARS-CoV-2 infection (https://investors.sorrentotherapeutics.com/news-releases/news-release-details/sorrento-releases-preclinical-data-sti-1499-covi-guardtm-and-sti). A phase 1 trial is ongoing in 33 participants (https://clinicaltrials.gov/ct2/show/NCT04454398?term=monoclonal+antibody&recrs=adefh&cond=COVID-19&draw=2&rank=29).

Vir Biotechnology and GlaxoSmithKline announced the initiation of a phase 2/3 study with VIR-7831 (also known as GSK4182136), a fully human anti-SARS-CoV-2 monoclonal antibody, for the early treatment of COVID-19 in patients who are at high risk of hospitalisation. The aim of the COMET-ICE study, which will enrol approximately 1300 patients worldwide who have early symptomatic infection, is to assess whether VIR-7831, as a single-dose monoclonal antibody, can prevent hospitalisation due to COVID-19 (https://www.gsk.com/en-gb/media/press-releases/vir-biotechnology-and-gsk-start-phase-23-study-of-covid-19-antibody-treatment/).

Among a few additional trials ongoing in China, a randomized, double-blind, placebo-controlled, phase I clinical study sponsored by Shanghai Junshi Bioscience evaluates the tolerability, safety, pharmacokinetic profile and immunogenicity of JS016 administered as a single intravenous infusion (https://clinicaltrials.gov/ct2/show/NCT04441918?term=antibody&recrs=adefh&type=Intr&cond=COVID-19&draw=1&rank=4).

Phytopharmaceuticals

Medicinal herbs have proven along history to be a source of multiple cures. A review by Huang (Front Pharmacol 2020, see ***below***) showed how exploring prophylactics from herbal medicine is probably a promising and practical strategy to contain the pandemic. Several natural compounds were described as potential SARS-CoV-2 viral inhibitor in molecular docking studies (Adhikari Phytother Res 2020, see ***below***), and others having anti-inflammatory properties that could potentially prevent COVID-19 complications in patients tested positive.

Eucalyptol (1,8 cineole), an essential oil component from eucalyptus oil, has the potential of inhibiting the main viral proteinase (Mpro/3CLpro) that is critical for the SARS-CoV-2 replication (Sharma, manuscript on Preprints: https://www.preprints.org/manuscript/202003.0455/v1). The artemisinin class of compounds was found to interact with SARS-CoV-2 Protein RBD with an antiviral effect (Sehailia J Biomol Struct Dyn 2020, see ***below***). A clinical study is currently conducted in Mexico to evaluate the benefit of *artemisia annua* and camostat mesylate in preventing COVID-19 complications in 360 patients with positive testing in mild to moderate disease and high-risk factors (NCT04530617).

Glycyrrhizin (an active component of licorice roots) has been shown to interfere with the replication and/or cytopathogenic effect of many respiratory viruses, including the replication of SARS-associated CoV (Cinatl Lancet 2003, see ***below***). The biological function of glycyrrhizin and its multisite mechanisms have been described *in vitro* and in animal experiments (Luo Int J Antimicr Ag 2020, see ***below***), showing potential benefits for COVID-19 including: a) Binding ACE2 to prevent SARS-CoV-2 infection. b) Downregulating proinflammatory cytokines. c) Inhibiting the accumulation of intracellular ROS. d) Inhibiting thrombin. e) Inhibiting the hyperproduction of airway exudates. f) Inducing endogenous interferon to combat the SARS-CoV-2. A clinical study conducted in Egyptian patients with COVID-19 is evaluating the potential therapeutic effects of Licorice and *Boswellia Serrata* Gum as a Complementary Medicine. *Boswellia serrata*, used in Ayurvedic medicine for inflammatory condition of the lung like asthma or allergy, has been shown to reduce lung inflammation in BALB/c mice (Soni Curr Drug Discov Technol 2020, see ***below***).

Originally extracted from *colchicum*, colchicine is an alcaloid and an anti-inflammatory drug that is usually prescribed to treat gout, chronic inflammatory disease like Behcet disease, and pericarditis. As the severe complications of COVID-19 are largely due to the patient's immune reactions, colchicine would reduce the complications associated with COVID-19 (Montealegre-Gómez Reumatol Clin 2020, see ***below***). Several clinical studies are underway to assess the effect of colchicine in covid-19 complications as well as its tolerance, among some of them are: the COLCORONA study (6000 high risk patients in Canada, NCT04322682), the GRECCO-19 study (180 patients in Greece, NCT04326790), the CONVINCE study (420 patients in Switzerland, NCT04516941), and the COLCOVID study (2500 patients in Argentina, NCT04328480).

A very recent publication reviewed phytopharmaceuticals derived from the traditional herbs that targets entry receptor of the host cells to block the interaction and attachment of some pathogenic viruses, and could potentially be useful in COVID-19 (Palit Phytomed 2020: https://www.sciencedirect.com/science/article/pii/S0944711320302270). Additional researches and clinical studies are necessary before utilizing those natural compounds in COVID-19 patient management.

Traditional Chinese Medicine

The utilization of Traditional Chinese Medicine (TCM) in managing COVID-19 is substantial in China. All confirmed COVID-19 cases in Shanghai started integrative Chinese-Western medicine treatment (Yuan and Qiu. Forty-one patients with new coronavirus pneumonia were treated with traditional Chinese medicine. Xinhua Net, Shanghai, 2020). The Diagnosis and Treatment Protocol issued by the National Health Commission of the People's Republic of China has been updated as additional research evidence and knowledge on COVID-19 have become available. Since the release of the first version of the protocol on January 15th, 2020, 7 versions in total have been produced with 8 updates over a 50-day period (Qiu 2020, see ***below***). The inclusion and elaboration on the use of TCMs in the Diagnosis and Treatment Protocol have been gradually improved. This National guideline has recommended herbal formulations according to clinical stages and severity of COVID-19. Although national/provincial/local guidelines could differ in terms of treatment strategy, most guidelines defined COVID-19 as endemic, toxic, dampness or warm infectious disease (Chan Am J Chin Med 2020, see ***below***). The six most commonly used herbs were *Astragali Radix* (Huangqi), *Glycyrrhizae Radix Et Rhizoma* (Gancao), *Saposhnikoviae Radix* (Fangfeng), *Atractylodis Macrocephalae Rhizoma* (Baizhu), *Lonicerae Japonicae Flos* (Jinyinhua), and *Forsythiae Fructus* (Lianqiao). Some of them are the core components of classical herbal formula: Yupingfeng san (powder), for tonifying qi to protect from external pathogens, and Yinqiao san (powder), used to prevent and treat respiratory infectious diseases (Luo Chin J Integr Med 2020, see ***below***). During an oral communication at the IDWeek, October 21-25 2020, Dr Gui-Qiang Wang (Department of Infection Disease, Peking University First Hospital) presented the most recent COVID-19 patient management in China. The Traditional Chinese Medicine treatment is used for the early management of patients with COVID-19 includes oral preparations of medicinal herbs, among them: *lianhua qingwen* capsules, *jinhua qiggan* granules, and *shufeng jiedu* capsules.

Clinical trials related to management of patients with COVID-19 19 that include evaluation of TCM were registered on the WHO's International Clinical Trials Registry Platform (ICTRP) (Aronson at https://www.cebm.net/oxford-covid-19/covid-19-registered-trials-and-analysis/).

Ayurveda

Wanjarkhedkar (J Ayurveda Integr Med 2020, see ***below***) reported the outcome of a prospective study conducted with a combination of Ayurvedic medications, as an add on, in 101 COVID-19 positive patients with mild to moderate symptoms. Patients receiving *Dasamoolkaduthrayam Kashaya* & *Guluchyadi Kwatham* in tablet form in addition to the standard of care showed a faster recovery from dyspnoea with reduced ageusia. Patients on the treatment group could be discharged earlier than those from the control group. However, as pointed out by Pathania (J Famil Med Prim Care 2020, see ***below***), studies are still lacking to support the use of Indian systems of medicine like Ayurveda against COVID-19. More randomized controlled trials need to be done. Of note, the authors noted that family physicians can play a vital role in not only suggesting treatment, but also changes in lifestyle of the patients as well as their family. As presented below in the section on ***Non-vaccine approaches to better host resistance***, Ayurveda is largely used as a means to increase immunity.

Host-directed therapies

An important area of research is focused on host-directed therapies targeting the underlying aberrant immune responses leading to pulmonary tissue damage, death, or long-term functional disability in survivors.

Therapies targeting acute respiratory distress syndrome

Acute respiratory distress syndrome is a common cause of respiratory failure in critically ill patients and is defined by the acute onset of non-cardiogenic pulmonary oedema, hypoxaemia and the need for mechanical ventilation (Matthay Nat Rev Dis Primers 2019, see ***below***). Despite some improvements, it remains associated with a high level of mortality (30-40%) in most studies. One approach to improve disease outcome is to identify patients earlier in their clinical course, so that supportive care with lung-protective ventilation, prone positioning and a conservative fluid approach can be implemented. Up to now, pharmacological agents did not prove very helpful in the management of acute respiratory distress syndrome. A review by Lewis (Cochrane Database Syst Rev 2019, see ***below***) found insufficient evidence to determine with certainty whether corticosteroids, surfactants, N-acetylcysteine, statins, or beta-agonists were effective at reducing mortality, or duration of mechanical ventilation, or at increasing ventilator-free days. The list of unsuccessful therapies also includes agents such as prostaglandin E1, activated protein C, anti-oxidants, omega-3 supplementation, ketoconazole, lisofylline, factor VIIa, IFN-β1α, or granulocyte macrophage-stimulating factor. However, it remains possible that the clinical trials that evaluated these products were not designed in the most suitable way.

Shi (Cell Death Diff 2020, see ***below***) suggested the use of intratracheal **hyaluronidase** to eliminate hyaluronan, known to be associated with ARDS. Even though the accumulation of hyaluronan has not been confirmed in COVID-19 cases yet, autopsies have concluded that the lungs are filled with clear liquid jelly. Aerosol administration of hyaluronidase had been considered before for ARDS (https://www.omicsonline.org/open-access/hyaluronidase-a-potential-new-treatment-for-acute-respiratory-distresssyndrome-2161-105X-1000407.php?aid=89111).

Solaimanzadeh (Cureus 2020, see ***below***) analysed clinical data published on COVID-19 in the context of another respiratory illness - high altitude pulmonary oedema (HAPE). The similarities between the 2 conditions led to the recommendation to evaluate **acetazolamide**, a drug that potently reduces hypoxic pulmonary vasoconstriction, improves minute ventilation and expired vital capacity. Other therapeutics to consider that are also directed towards decreased pulmonary pressure include Nifedipine and Phosphodiesterase inhibitors.

There is evidence in both animals and humans that fibrinolytic therapy in acute lung injury and ARDS improves survival. There would be a rationale for such therapeutic approach in patients with ARDS and concomitant diagnoses of disseminated intravascular coagulation, as observed in more than 70% of those who die of COVID-19. Wang (J Thromb Haemost 2020, see ***below***) reported 3 cases of off-label intravenous administration of **tissue plasminogen activator** (Alteplase) for patients with COVID-19 suffering from ARDS and respiratory failure. In all 3 cases the patients demonstrated an initial improvement in their PaO2/FiO2 ratio, with improvements ranging from a 38% improvement to a ~100% improvement. However, the observed improvements were transient in all 3 patients.

Whereas it is reported that plasminogen is dramatically increased in adults with ARDS, Wu (QJM 2020, see ***below***) treated 13 clinically moderate, severe or critical COVID-19 patients with atomization inhalation of freeze-dried **plasminogen**. After plasminogen inhalation, conditions of lung lesions in 5 clinically moderate patients quickly improved, as shown by the decreased range and density of 'ground glass' opacity. Improvements of oxygen saturation were observed in 6 clinically severe patients. In the 2 patients with critical conditions, the oxygen levels significantly increased from 79-82% to 91% just about 1 hour after the first inhalation. In 8 of 13 patients heart rates slowed down. Furthermore, a general relief of chest tightness was observed. Overall, the study suggested that additional plasminogen may be effective and efficient in treating lung lesions and hypoxemia during COVID-19 infections. Further studies are now needed to confirm this observation.

Blood purification systems

A short review by Keith (Crit Care 2020, see ***below***) provided the rationale as well as preliminary data supporting **total plasma exchange** in patients with sepsis and multiple organ failure (not related to COVID-19). To what extent this

approach may be successful in the management of patients with the most severe forms of COVID-19 remains to be confirmed.

An **artificial-liver blood-purification system** is reported to have shown good prognosis in the treatment of severely or critically ill COVID-19 patients with cytokine storm (Zhang Engineering 2020, see ***below***). Based on the above-described evidence, the Expert Consensus on the Application of Artificial-Liver Blood-Purification System in the Treatment of Severe COVID-19 was recently released. This work recommends artificial-liver blood purification for the treatment of patients with COVID-19 infection who exhibit cytokine storm and rapid disease progression, as confirmed by lung imaging.

Noting that renal replacement therapy in combination with sequential **extracorporeal blood purification** therapies might support renal function, attenuate systemic inflammation, and prevent or mitigate multiple organ dysfunctions in COVID-19, Villa (Crit Care 2020, see ***below***) conducted a preliminary observational prospective study assessing the outcome of 37 patients with COVID-19 admitted to the ICU and treated with extracorporeal blood purification according to local practice. Extracorporeal blood purification with heparin-coated hemodiafilter featuring cytokine adsorption properties (oXiris membrane) showed to be feasible and with no adverse events in patients with COVID-19. During the treatment, patients experienced serum IL-6 level reduction, attenuation of systemic inflammation, multiorgan dysfunction improvement, and reduction in expected ICU mortality rate.

Another relevant publication on this topic is the report by Akil (Thorac cardiovasc Surg 2020, see ***below***) of a small study conducted before the COVID-19 epidemic, where combined high-flow venovenous ECMO and **CytoSorb hemoadsorption therapy** (CytoSorb filter connected to ECMO circuit) were applied in 13 patients with pneumogenic sepsis and ARDS. All patients survived in the CytoSorb group, while the 30-day mortality rate reached 57% in the control group. After CytoSorb therapy, a significant reduction in procalcitonin and CRP levels was immediately observed. CytoSorbents' purification technologies are based on biocompatible, highly porous polymer beads that can actively remove toxic substances from blood and other bodily fluids by pore capture and surface adsorption.

Cell-based therapies

Meng (Signal Transduct Target Ther 2020, see ***below***) performed a parallel assigned controlled, non-randomized, phase 1 clinical trial to evaluate the safety of human umbilical cord-derived mesenchymal stem cells (UC-MSCs) infusions in the treatment of patients with moderate and severe COVID-19 pulmonary disease. The study enrolled 18 hospitalized patients with COVID-19 (n = 9 for each group). The treatment group received three cycles of intravenous infusion of UC-MSCs (3×10^7 cells per infusion) on days 0, 3, and 6. Both groups received standard COVID-treatment regimens. Adverse events, duration of clinical symptoms, laboratory parameters, length of hospitalization, serial chest CT images, the PaO2/FiO2 ratio, dynamics of cytokines, and IgG and IgM anti-SARS-CoV-2 antibodies were analysed. No serious UC-MSCs infusion-associated adverse events were observed. Two patients receiving UC-MSCs developed transient facial flushing and fever, and one patient developed transient hypoxia at 12 h post UC-MSCs transfusion. Mechanical ventilation was required in one patient in the treatment group compared with four in the control group. All patients recovered and were discharged. These data suggest that intravenous UC-MSCs infusion in patients with moderate and severe COVID-19 is safe and well tolerated, but phase 2/3 randomized, controlled, double-blinded trials with long-term follow-up are needed to evaluate the therapeutic use of UC-MSCs in patients with serious COVID-19.

Ozone therapy

A review by Martínez-Sánchez (Antioxidants 2020, see ***below***) suggested that systemic ozone therapy could be potentially useful in the clinical management of several complications secondary to SARS-CoV-2 infection. Ozone therapy usually consists of an *ex vivo* procedure called autohemotherapy. For instance, 100mL of blood is drawn from the patient into a sterile glass bottle with anticoagulant. A corresponding volume of gas with an ozone concentration of 10-20 µg/mL is immediately added and continuously mixed. Reinfusion is then performed within about 15-20

minutes. The procedure is repeated two or three times a week. The rationale and mechanism of action of ozone therapy has been previously studied in other viral infections and shown effective at decreasing organ damage mediated by inflammation and oxidative stress.

Tascini (Intern Emerg Med 2020, see ***below***) used auto-hemotherapy treated with an oxygen/ozone (O2/O3) gaseous mixture as adjuvant therapy for COVID-19 in Udine University Hospital (Italy). The authors reported a case-control study involving 60 hospitalized adult patients with confirmed COVID-19 with mild to moderate pneumonia. The study data suggested that O2/O3 therapy as adjuvant therapy could be useful in mild to moderate pneumonia due to SARS-CoV-2. Several clinical evaluations of ozone have been reported as ongoing, targeting either COVID-19 therapy (e.g. NCT04366089, NCT04388514) or prophylaxis (NCT04400006, in 71 participants only).

Local disinfection

The nose and the mouth represent entry portals for SARS-CoV-2. Nasal irrigations can reduce the viral load in the nasal cavities. Oral rinse with antimicrobial agents is efficacious in reducing the viral load in oral fluids (Casale Int J Immunopathol Pharmacol 2020, see ***below***). Various authors advocate the inclusion of nasal irrigations and oral rinses as additional measures to current public health measures, to prevent and control the transmission of any respiratory infectious disease, including COVID-19.

Oral hygiene

Pattanshetty (Oral Dis 2020, see ***below***) suggested oral hygiene as a quite novel approach to reduce COVID-19 transmission. The proposal is based on several previous reports suggesting for instance that povidone-iodine (PVP-I) products in the form of mouthwashes and throat sprays had a prophylactic effect on SARS-CoV transmission. The importance of oral hygiene interventions, including gel/mouthwash, standard oral care and professional oral hygiene protocols in reducing the risk of pneumonia had been documented long before the COVID-19 epidemic. And a more recent line of evidence was obtained from post-hoc secondary analysis of data from the Edinburgh and Lothians Viral Intervention Study (ELVIS) pilot randomised controlled trial indicated that hypertonic saline nasal irrigation and gargling reduced the duration of coronavirus upper respiratory tract infection by an average of two-and-a-half days (Ramalingam J Glob Health 2020, see ***below***). The authors suggested that it may offer a potentially safe, effective and scalable intervention in those with COVID-19.

It has been suggested that the measures for controlling SARS-CoV-2 cross-infection during dental practice should include a preprocedural mouth rinse containing oxidative agents such as 1% hydrogen peroxide and 0.2% PVP-I. This protocol, with small variations, has been accepted by the main professional dental associations worldwide. Considering that there is no reason to limit this approach to the dental clinic setting, Martínez Lamas (Oral Dis 2020, see ***below***) suggested a routine administration of such mouth rinses to the entire population to prevent community transmission of SARS-CoV-2.

From a literature search, Herrera (Clin Oral Investig. 2020, see ***below***) even suggested that antiseptic mouth rinses, such as those containing cetylpyridinium chloride or povidone-iodine, may be able to decrease the severity of COVID-19 by reducing oral viral load in infected subjects. Nevertheless, well-designed clinical and preclinical research must be conducted to support these hypotheses.

Meister examined the *in vitro* virucidal activity of 8 commercially available oral rinses using a quantitative suspension test with 3 different SARS-CoV-2 isolates mixed with an interfering substance mimicking a respiratory secretion (J Inf Dis 2020, see ***below***). The different SARS-CoV-2 strains were highly susceptible to various oral rinses. Three of the 8 formulations significantly reduced viral infectivity to up to 3 orders of magnitude to background levels. Also, for the other products containing different active compounds, virucidal activities could be observed with log reduction factors ranging between 0.3 to 1.78.

Martínez Lamas (Oral Dis 2020, see ***below***) analysed the impact of a mouthwash with PVP-I on the salivary virus load in 4 patients with COVID-19. A significant drop in salivary viral load, which remained for at least 3 hr, was observed in 2/4 patients. Of note, the PCR of the nasopharyngeal exudate of these 2 patients was negative at baseline. These preliminary findings remain insufficient to draw any conclusion as to the clinical efficacy of an antiseptic mouthwash to control the transmission of SARS-CoV-2. The likely impact of a daily use of mouth rinses containing antiseptics for limited periods of time (e.g., when being a carrier of the virus) on the viral transmissivity remains to be better explored.

From a search on June 1st 2020, Burton (Cochrane Database Syst Rev 2020, see ***below***) found no completed studies to include in their Cochrane review. The authors identified 16 ongoing studies (including 14 RCTs), which aim to enrol nearly 1250 participants. The interventions included in these trials are ArtemiC (artemisinin, curcumin, frankincense and vitamin C), Citrox (a bioflavonoid), cetylpyridinium chloride, chlorhexidine, chlorine dioxide, essential oils, hydrogen peroxide, hypertonic saline, Kerecis spray (omega 3 viruxide - containing neem oil and St John's wort), neem extract, nitric oxide releasing solution, povidone iodine and saline with baby shampoo. The authors were concerned that few of the ongoing studies specifically stated that they will evaluate adverse events such as changes in the sense of smell or to the oral and nasal microbiota, and any consequences thereof. If a positive treatment effect is demonstrated, it may indeed not be large. In these circumstances the authors consider that it may be a challenge to weigh up the benefits against the harms if the latter are of uncertain frequency and severity.

Nasal wash

The technique of nasopharyngeal wash to prevent virus from inhabiting and replicating in the nasal and pharyngeal mucosa has been suggested to be useful in reducing symptoms, transmission, and viral shedding in cases of acute respiratory tract infections. In a rapid systematic review, Singh (Lung India 2020, see ***below***) found studies showing some improvement in prevention and treatment of upper respiratory tract infections. The authors postulated that hypertonic saline gargles and nasal wash may be useful in prevention and for care of patients with COVID-19. The present evidence emphasizes the need of randomized controlled trials to evaluate the role and mechanism of nasopharyngeal wash in COVID-19.

Inhalation of acetic acid

Pianta (Eur Arch Otorhinolaryngol. 2020, see ***below***) indicated that inhalation of a water-based acetic acid solution to treat the symptoms of the common cold is a common folk remedy in Italy. Indeed, the anti-bacterial and anti-viral activities of acetic acid are documented in the literature. Acetic acid causes inactivation and dis-aggregation of haemagglutinin glycoproteins (found on the surface of influenza viruses) by generating a low pH-dependent conformational change of those glycoproteins and it destroys the viral envelope and inhibits viral transmission. Therefore, the authors explored the use of this historical therapy in a small group of patients with early-stage COVID-19. In this exploratory study, patients treated with acetic acid that experienced improvement in individual symptoms was double that of the other group of patients, although numbers were too small for robust statistical analysis.

Vaccine development

Overview

Vaccines in development

Within two months of the COVID-19 outbreak, at least 37 biopharmaceutical companies or academic sectors were reported to be in the race to develop a prophylactic vaccine by using several platforms including mRNA, DNA, adenoviral vector and recombinant protein (Prompetchara Asia Pac J All Imm 2020, see ***below***). However, the number of vaccine projects soon increased. A draft landscape of the candidate SARS-CoV-2 vaccines under development has been provided by WHO (last updated on October 19 2020): https://www.who.int/who-documents-detail/draft-

landscape-of-covid-19-candidate-vaccines. As of October 19 2020, the dashboard of the London School of Hygiene and Tropical Medicine (https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/) described a total of 248 vaccine candidates, including 49 candidates in clinical trial testing phase. As presented in ***Table 14***, numerous vaccine candidates have reached phase 1 or 1/2 clinical trial testing stage of development, and phase 3 is ongoing for a total of eleven candidates (2 RNA, 1 subunit, 4 non-replicating viral vectors, and 4 inactivated vaccines).

Table 14 Vaccine candidates in clinical development as of October 6 2020*

Platform	Candidate vaccine	Clinical trial number	Clinical phase	N
RNA	BNT162 (BioNTech/Pfizer)	NCT04368728	Phase 1/2/3	43998
		NCT04380701	Phase 1/2	456
		NCT04523571	Phase 1	144
		NCT04537949	Phase 1/2	120
	mRNA-1273 (Moderna)	NCT04283461	Phase 1	120
		NCT04405076	Phase 2	600
		NCT04470427	Phase 3	30000
	CVnCoV (Curevac)	NCT04449276	Phase 1	168
		NCT04515147	Phase 2	691
	LNP-nCoVsaRNA (Imperial College)	ISRCTN17072692	Phase 1	320
	ARCT-021 (Arcturus)	NCT04480957	Phase 1/2	92
DNA	INO-4800 (Inovio)	NCT04336410	Phase 1	120
		NCT04447781	Phase 1/2	160
	GX-19 (Genexine)	NCT04445389	Phase 1/2	210
	ZyCoV-D (Zydus Cadila)	CTRI/2020/07/026352	Phase 1/2	1048
	AG0301-COVID19 & AG0302-COVID19 (Osaka University/ AnGes/ Takara Bio)	NCT04463472	Phase 1/2	30
		NCT04527081	Phase 1/2	30
Subunit	NVX-CoV2373 +/- MATRIX-M™ (Novavax)	NCT04368988	Phase 1/2	1419
		NCT04533399	Phase 2	2904
		2020-004123-16	Phase 3	9000
	CoVLP (Medicago)	NCT04450004	Phase 1	180
	(SpyBiotech/Serum Institute of India)	ACTRN12620000817943	Phase 1/2	280
	Covax-19 (Vaxine/Medytox)	NCT04453852	Phase 1	40
	SCB-2019 (Clover)	NCT04405908	Phase 1	150
	V451 (University of Queensland/CSL/Seqirus)	ACTRN12620000674932p (NCT04495933)	Phase 1	216
	AdimrSC-2f (AdImmune)	NCT04522089	Phase 1	70
	EpiVacCorona (Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector")	NCT04527575	Phase 1/2	100
	(Sanofi Pasteur, GSK)	NCT04537208	Phase 1/2	440
	UB-612 (Covaxx/Uni Nebraska)	NCT04545749	Phase 1	60
	(Finlay Institute)	IFV/COR/04	Phase 1/2	676
	(Anhui Zhifei Longcom Biopharmaceutical/Chinese Academy of Sciences)	NCT04445194	Phase 1	50
		NCT04550351	Phase 1/2	50
		NCT04466085	Phase 2	900
Vector	AZD1222 (AstraZeneca)	NCT04324606	Phase 1/2	1090
		NCT04400838 (2020-001228-32)	Phase 2/3	12390
		ISRCTN89951424	Phase 3	2000
		NCT04444674	Phase 1/2	2000
		NCT04536051	Phase 3	5000
		NCT04568031	Phase 1/2	12
		CTRI/2020/08/027170	Phase 2/3	1600
	Adenovirus Type 5 Vector (CanSino)	NCT04313127 (ChiCTR2000030906)	Phase 1	108
		NCT04341389 (ChiCTR2000031781)	Phase 2	508
		NCT04568811	Phase 1	89
		NCT04526990	Phase 3	40000
		NCT04540419	Phase 3	500
		NCT04566770	Phase 2	481

Platform	Candidate vaccine	Clinical trial number	Clinical phase	N
	Ad5-nCoV (Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China)	NCT04552366	Phase 1	144
	VXA-CoV2-1 (Vaxart)	NCT04563702	Phase 1	48
	Ad26.COV2.S (Janssen Vaccines & Prevention)	NCT04436276 NCT04509947 NCT04505722	Phase 1/2 Phase 1 Phase 3	1045 250 60000
	Gam-COVID-Vac (Gamaleya Research Institute)	NCT04436471 NCT04437875 NCT04564716 NCT04530396	Phase 1 Phase 1 Phase 3 Phase 3	38 38 100 40000
	GRAd-COV2 (ReiThera/Leukocare/Univercells	NCT04528641	Phase 1	90
	V591 (Institut Pasteur/Themis/University of Pittsburg/Merck)	NCT04497298 NCT04498247	Phase 1 Phase 1/2	90 260
Inactivated	Sinovac/Butantan	NCT04352608 NCT04383574 NCT04456595 NCT04508075 NCT04582344	Phase 1/2 Phase 1/2 Phase 3 Phase 3 Phase 3	744 422 8870 1620 13000
	Beijing Institute of Biological Products/Sinopharm	ChiCTR2000032459 ChiCTR2000034780 NCT04560881	Phase 1/2 Phase 3 Phase 3	2128 15000 3000
	Wuhan Institute of Biological Products/Sinopharm	ChiCTR2000031809 ChiCTR2000034780 NCT04510207	Phase 1/2 Phase 3 Phase 3	1456 15000 45000
	BBV152/Covaxin (inactivated, Bharat Biotech)	CTRI/2020/07/026300 (NCT04471519) CTRI/2020/09/027674	 Phase 1/2 Phase 1/2	 755 124
	Institute of Medical Biology, Chinese Academy of Medical Sciences	NCT04412538 NCT04470609	Phase 1 Phase 1/2	942 471
	QazCovid-in (inactivated, Research Institute for Biological Safety Problems)	NCT04530357	Phase 1/2	244
Cell-based	aAPC (Shenzhen Geno-Immune Medical Institute)	NCT04299724	Phase 1	100
	LV-SMENP-DC (Shenzhen Geno-Immune Medical Institute)	NCT04276896	Phase 1	100

* *All studies included in this table have recruited or are recruiting participants*

Another overview of the various COVID-19 vaccines under development (including planned vaccine manufacturing capacity and key business information) can be found at https://racap.com/covid-19 (last accessed on October 19 2020).

A Target Product Profile (TPP), issued by WHO in April 2020, described the preferred and minimally acceptable profiles for human vaccines for long term protection of persons at high ongoing risk of COVID-19 such as healthcare workers as well as for reactive use in outbreak settings with rapid onset of immunity (https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines).

Full-length S or S1 which contains receptor binding domain (RDB) have been considered as a candidate vaccine antigens as they induce neutralizing antibodies preventing host cell attachment and infection. The S antigen has been included in different types of vaccines against infections by CoVs (Yu Micr Inf 2020, see ***below***). Conserved B cell and T cell epitopes between SARS-CoV and SARS-CoV-2 were also found in the viral nucleocapsid (N) protein (Ahmed Viruses 2020 see ***below***, Grifoni Cell Host & Microbe 2020, see ***below***).

An illustrative landscape on the development of coronavirus vaccines has been provided in a Nature's news feature by Callaway (Nature 2020, see ***below***). However, the review is by Poland (Mayo Clin Proc 2020, see ***below***) on this topic is more up-to-date.

Probability of success

Lu (Emerg Microbes Inf 2020, see ***below***) described both the reasons why a COVID-19 vaccine is needed, and the challenges to be faced. Likewise, Amanat and Krammer gave their perspective on the development of SARS-CoV-2 vaccines and its challenges (Immunity 2020, see ***below***).

Building on experience from the past, various authors have highlighted a list of criteria that can help predict the likelihood of success of research towards vaccines against novel infectious diseases. Satterfield (Vaccine 2016, see ***below***) for instance, identified a set of criteria while discussing the biological feasibility of a vaccine against Nipah. Additional criteria can be identified from the decision guide provided by the Medical Research Council in the U.K. (http://vaccinedevelopment.org.uk/decision-guide.html).

- Complexity and size of pathogen
- Little genetic (antigenic) diversity, low mutation rate
- The pathogen can be cultured in vitro
- Vaccine available against a closely related pathogen
- Incubation period of the disease of at least 5-7 days
- Reported cases of natural immunity, both durable and protective
- Passive transfer of neutralizing antibodies known to be protective
- Available animal models, including human challenge models

More recently, in considering the "certainty of success" in development of SARS-CoV-2 vaccines, Kaslow (NPJ Vaccines 2020, see ***below***) proposed a third, related critical parameter - the infectious inoculum intensity, at an individual-level, and force of infection, at a population-level. Reducing the infectious inoculum intensity (and force of infection, at a population-level) is indeed predicted to lengthen the incubation period, which in turn is predicted to reduce the severity of illness, and increase the opportunity for an anamnestic response upon exposure to the circulating virus. Similarly, successfully implementing individual- and population-based behaviours that reduce the infectious inoculum intensity and force of infection, respectively, while testing and deploying COVID-19 vaccines is predicted to increase the "certainty of success" of demonstrating vaccine efficacy and controlling SARS-CoV-2 infection and the pandemic itself.

Of note, all of these success criteria focused on vaccine efficacy/effectiveness. Vaccine safety upon large scale utilization is obviously of utmost importance in the case of COVID-19, even though the criteria that could help predict such safety seem more difficult to identify. Su (Nature Rev Microb 2020, see ***below***) provided an important perspective on this topic by summarizing examples of vaccine-associated disease enhancement in the history of developing vaccines against respiratory syncytial virus, dengue virus, SARS-CoV and MERS-CoV, highlighting the importance of a robust safety and efficacy profile.

RNA vaccines

Moderna, Inc. and the Coalition for Epidemic Preparedness Innovations (CEPI) announced a new collaboration to develop an mRNA vaccine against COVID-19 (https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-funding-award-cepi-accelerate-development). Under the terms of the agreement, Moderna will manufacture an mRNA vaccine, which will be funded by CEPI. The Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID) collaborated with Moderna to design the vaccine. The mRNA-1273 vaccine candidate encodes the S-2P antigen, consisting of the SARS-CoV-2 glycoprotein with a transmembrane anchor and an intact S1–S2 cleavage site (Jackson NEJM 2020, see ***below***). S-2P is stabilized in its prefusion conformation by two consecutive proline substitutions at amino acid positions 986 and 987, at the top of the central helix in the S2 subunit.

Corbett (manuscript on medRxiv, see https://www.biorxiv.org/content/10.1101/2020.06.11.145920v1) presented data indicating that mRNA-1273 induces both potent neutralizing antibody and CD8 T cell responses in mice. As highlighted by Vabret (Nature Rev Imm 2020, see ***below***), two doses of the candidate vaccine given in prime-boost combination (2 x 1 µg/mouse) protected mice against infection of the nasal mucosa and lungs after challenge with mouse-adapted SARS-CoV-2. Importantly, there was no indication of enhanced immunopathology in animals that received sub-protective doses.

Moderna announced the initiation of the phase 1 trial of the mRNA-1273 vaccine on March 16 (https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-first-participant-dosed-nih-led-phase-1-study; study NCT04283461). The vaccine candidate mRNA-1273 consists of lipid nanoparticles packaged with nucleoside-modified mRNA that encodes a prefusion-stabilized form of the SARS-CoV-2 S protein. Three dose levels of mRNA-1273 (25, 100, 250 µg) were administered on a two-dose vaccination schedule, given 28 days apart. A total of 45 healthy adults were enrolled in the study. Participants are to be followed through 12 months after the second vaccination. Preliminary results from the trial were disclosed by Jackson (NEJM 2020, see ***below***). Solicited adverse events that occurred in more than half the participants included fatigue, chills, headache, myalgia, and pain at the injection site. Systemic adverse events were more common after the second vaccination, particularly with the highest dose, and three participants (21%) in the 250-µg dose group reported one or more severe adverse events. After the first vaccination, antibody responses were higher with higher dose (day 29 enzyme-linked immunosorbent assay anti–S-2P antibody geometric mean titer [GMT], 40 227 in the 25-µg group, 109 209 in the 100-µg group, and 213 526 in the 250-µg group). After the second vaccination, the titers increased (day 57 GMT, 299 751, 782 719, and 1 192 154, respectively). After the second vaccination, serum-neutralizing activity was detected by two methods in all participants evaluated, with values generally similar to those in the upper half of the distribution of a panel of control convalescent serum specimens. Data obtained from 40 additional participants of older age were reported by Anderson (NEJM 2020, see ***below***). Binding- and neutralizing-antibody responses appeared to be similar to those previously reported among vaccine recipients between the ages of 18 and 55 years and were above the median of a panel of controls who had donated convalescent serum. The vaccine elicited a strong CD4 cytokine response involving type 1 helper T cells.

A phase 2 clinical trial is ongoing, which compares vaccine doses of 50 and 100 µg in young vs. older adults (total size of 600 study participants) (https://clinicaltrials.gov/ct2/show/NCT04405076?term=mRNA-1273&draw=2&rank=1). A phase 3 efficacy trial was initiated on July 27th (https://www.nih.gov/news-events/news-releases/phase-3-clinical-trial-investigational-vaccine-covid-19-begins).

Curevac and CEPI also announced a collaboration to develop a vaccine against COVID-19 based on CureVac's technology and mRNA platform (https://www.curevac.com/news/curevac-and-cepi-extend-their-cooperation-to-develop-a-vaccine-against-coronavirus-ncov-2019#). CureVac indicated that their mRNA platform using lipid nanoparticles in phase 1 study for the prevention of rabies was capable of providing protective virus-neutralizing antibody titers after two vaccination with dose of 1µg mRNA vaccine (https://www.curevac.com/news/curevac-announces-positive-results-in-low-dose-1-%C2%B5g-rabies-vaccine-clinical-phase-1-study). The company received regulatory approval from the German and Belgian authorities in June 2020 to initiate Phase 1 clinical trial of its SARS-CoV-2 vaccine candidate (https://www.curevac.com/en/2020/06/17/curevac-receives-regulatory-approval-from-german-and-belgian-authorities-to-initiate-phase-1-clinical-trial-of-its-sars-cov-2-vaccine-candidate/l). A phase 2 trial is currently recruiting participants in Panama and Peru (NCT04515147).

BioNTech and **Pfizer** collaborate on the development of a mRNA-based vaccine candidate aimed at preventing COVID-19 (https://investors.biontech.de/news-releases/news-release-details/pfizer-and-biontech-co-develop-potential-covid-19-vaccine), building on a joined programme initiated by BioNTech and Pfizer in 2018 for the development of an influenza mRNA vaccine. The BNT162 program is evaluating at least four experimental vaccine candidates, each of

which represents a unique combination of mRNA format and target antigen. On May 5, Pfizer Inc. and BioNTech SE announced that the first participants have been dosed in the U.S. in the Phase 1/2 clinical trial of BNT162. This Phase 1/2 study was designed to determine the safety, immunogenicity and optimal dose level of the four mRNA vaccine candidates. The dose level escalation portion (Stage 1) of the Phase 1/2 trial in the U.S. was to enroll up to 360 healthy subjects into two age cohorts (18-55 and 65-85 years of age) (https://www.pfizer.com/news/press-release/press-release-detail/pfizer_and_biontech_dose_first_participants_in_the_u_s_as_part_of_global_covid_19_mrna_vaccine_development_program). Data from 45 healthy adults, 18 to 55 years of age, randomized to receive 2 doses of 10 µg, 30 µg, or 100 µg of BNT162b1, have been reported by Mulligan (Nature 2020, see ***below***). Local reactions and systemic events were dose-dependent, generally mild to moderate, and transient. A second vaccination with 100 µg was not administered due to increased reactogenicity and a lack of meaningfully increased immunogenicity after a single dose compared to the 30 µg dose. RBD-binding IgG concentrations and SARS-CoV-2 neutralizing titers in sera increased with dose level and after a second dose. Geometric mean neutralizing titers reached 1.9- to 4.6-fold that of a panel of COVID-19 convalescent human sera at least 14 days after a positive SARS-CoV-2 PCR. Sahin (Nature 2020, see ***below***) presented antibody and T-cell responses after BNT162b1 vaccination from a second, non-randomized open-label phase 1/2 trial in healthy adults, 18-55 years of age. Two doses of 1 to 50 µg of BNT162b1 elicited robust CD4+ and CD8+ T-cell responses and strong antibody responses, with RBD-binding IgG concentrations clearly above those in a COVID-19 human convalescent sample panel. Day 43 SARS-CoV-2 serum neutralising geometric mean titers were 0.7-fold (1 µg) to 3.5-fold (50 µg) those of the convalescent panel. Immune sera broadly neutralised pseudoviruses with diverse SARS-CoV-2 spike variants. Most participants had T helper type 1 skewed T cell immune responses with RBD-specific CD8+ and CD4+ T-cell expansion. IFNγ was produced by a high fraction of RBD-specific CD8+ and CD4+ T cells.

Pfizer and BioNTech have chosen to advance the BNT162b2 vaccine candidate into the Phase 2/3 study, at a 30 µg dose level in a 2 dose regimen. Enrolment of a planned cohort of 32 000 volunteers is currently ongoing (https://clinicaltrials.gov/ct2/show/NCT04368728). BNT162b2 received U.S. FDA Fast Track designation (https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-granted-fda-fast-track-designation-two). BioNTech also initiated an alliance with Fosun Pharma to conduct clinical trials in China.

A phase 1 clinical trial of a RNA vaccine candidate has been announced by **Walvax Biotechnology**, a Chinese company (https://www.yicaiglobal.com/news/china-gives-go-ahead-for-first-covid-19-mrna-vaccine-trial-; http://www.chictr.org.cn/showprojen.aspx?proj=55524).

Translate Bio also announced a collaboration with Sanofi Pasteur on a new mRNA COVID-19 vaccine (https://investors.translate.bio/news-releases/news-release-details/sanofi-pasteur-and-translate-bio-collaborate-develop-novel-mrna). On August 25 2020, a company presentation indicated that two injections of the mRNA/LNP vaccine candidate induced neutralizing antibodies and a TH1-biased T-cell responses (https://www.sec.gov/Archives/edgar/data/1693415/000119312520229383/d904716dex991.htm).

Self-amplifying RNA vaccines

A type of mRNA that has shown extraordinary properties to induce immune responses is the so-called self-amplifying RNA (saRNA). saRNA is derived from the genome of certain viruses like alphaviruses and flaviviruses and has the capacity of self-amplification due to the fact that it expresses a viral replicase (Rep), while the genes coding for the viral structural proteins have been substituted by the transgene of interest. As reviewed by Ballesteros-Briones (Curr Opin Virol 2020, see ***below***), most saRNAs used in vaccination studies derive from alphaviruses, including Venezuelan equine encephalitis virus, Semliki Forest virus, and Sindbis virus.

The **Imperial College** in London works on a mRNA COVID-19 vaccine candidate based on Venezuelan equine encephalitis virus **self-amplifying** RNA (saRNA) encapsulated in lipid nanoparticles. Encoding a pre-fusion stabilized

SARS-CoV-2 S protein, this self-amplifying mRNA vaccine was capable to elicit cellular responses and robust antibody responses in mice, showing neutralizing capacity of a pseudotyped SARS-CoV-2 virus (McKay Nature Comm 2020, see ***below***). A phase 1 trial of the candidate is reported as ongoing in the U.K. (http://www.isrctn.com/ISRCTN17072692).

Another self-replicating (replicon) mRNA that encodes for the prefusion S protein of SARS-CoV-2 was formulated in a lipid nanoparticle (**Arcturus Therapeutics**). De Alwis reported the positive outcome of immunogenicity experiments conducted in mice, with 100% of the animals developing a robust serological response after single dose vaccination and a dominance of TH1 response (manuscript on bioRxiv : https://www.biorxiv.org/content/10.1101/2020.09.03.280446v1). The investigational vaccine, ARCT-021, is undergoing phase 1/2 clinical evaluation (https://clinicaltrials.gov/ct2/show/NCT04480957?term=vaccine&cond=covid-19&draw=10).

A third candidate based on Venezuelan equine encephalitis virus saRNA expressing SARS-CoV-2 S encapsulated with Lipid InOrganic Nanoparticles (LION) has been developed by the University of Washington in partnership with HDT Bio Corp. This vaccine was able to induce neutralizing antibodies in old mice, as well as in nonhuman primates that lasted for at least 70 days (Erasmus Sci Transl Med 2020, see ***below***). According to HDT Bio communication, HDT-301 vaccine for COVID-19 is now preparing for IND filing (https://www.hdt.bio/news).

Pfizer in partnership with BioNtech has also developed a saRNA prototype vaccine, although the details of this vector/formulation have not been disclosed yet.

DNA vaccines

A study by Yu (Science 2020, see ***below***) provided encouraging data supporting the feasibility of a DNA vaccine against COVID-19 as early as in May 2020. The authors developed a series of DNA vaccine candidates expressing different forms of the SARS-CoV-2 S protein and evaluated them in 35 rhesus macaques. Vaccinated animals developed humoral and cellular immune responses, including neutralizing antibody titres comparable to those found in convalescent humans and macaques infected with SARS-CoV-2. Following vaccination, all animals were challenged with SARS-CoV-2, and the vaccine encoding the full-length S protein resulted in >3.1 and >3.7 log10 reductions in median viral loads in bronchoalveolar lavage and nasal mucosa, respectively, as compared with sham controls. Protection was likely not sterilizing but instead appeared to be mediated by rapid immunologic control following challenge. Vaccine-elicited neutralizing antibody titers correlated with protective efficacy, suggesting an immune correlate of protection. Several DNA vaccine candidates are currently undergoing clinical evaluation.

Inovio Pharmaceuticals, Inc. announced that it is developing INO-4800, a vaccine against COVID-19 based on the company's DNA platform with the support of CEPI (http://ir.inovio.com/news-and-media/news/press-release-details/2020/Inovio-Collaborating-With-Beijing-Advaccine-To-Advance-INO-4800-Vaccine-Against-New-Coronavirus-In-China/default.aspx). The Phase 1 study of INO-4800, reported to have started on April 3rd, enrolled 120 healthy adult volunteers to receive 1 or 2 injections per visit of INO-4800 administered intradermally followed by electroporation using CELLECTRA® 2000 device, on day 0 and week 4 (https://clinicaltrials.gov/ct2/show/NCT04336410). An ongoing phase 1/2 trial started on July 15. Of note, Inovio announced that the U.S. FDA has notified the company it has additional questions about the company's planned Phase 2/3 trial of INO-4800, including the CELLECTRA® 2000 delivery device to be used in the trial. Until the FDA's questions have been satisfactorily addressed, INOVIO's Investigational New Drug Application for the Phase 2/3 trial is on partial clinical hold (http://ir.inovio.com/news-releases/news-releases-details/2020/INOVIO-Reports-FDA-Partial-Clinical-Hold-for-Planned-Phase-2--3-Trial-of-COVID-19-Vaccine-Candidate-INO-4800/default.aspx). The company also announced that it is collaborating with Beijing Advaccine Biotechnology Co. to advance the vaccine candidate development in China. The goal of this collaboration is to leverage Advaccine's expertise to run a Phase 1 trial in China in parallel with Inovio's clinical development efforts in the U.S. Inovio and Advaccine will also work together to attract

additional grant funding and further collaborations with larger vaccine companies in China to increase the speed of future testing of INO-4800.

Another candidate under clinical evaluation is GX-19, the DNA vaccine candidate developed by Genexine, Inc (http://www.genexine.com/m62_view.php?idx=157&cate=1&year=). A phase 1/2 study is ongoing in a total of 210 subjects. The phase 2a part of the trial has a randomized, double-blind, placebo controlled design (https://clinicaltrials.gov/ct2/show/NCT04445389?term=antibody&recrs=adefh&type=Intr&cond=COVID-19&draw=1&rank=61).

On August 6 2020, India's Zydus Cadila said its COVID-19 vaccine candidate (ZyCoV-D) was found to be safe and well-tolerated in an early-stage human trial (https://zyduscadila.com/public/pdf/pressrelease/Press-Release-ZyCoV-D.pdf). Enrollment in a phase 2 study followed in over 1000 healthy adult volunteers as part of the adaptive phase I/II dose escalation, multicentric, randomized, double-blind placebo controlled study of the company (CTRI/2020/07/026352).

Subunit vaccines

Virus-like particles (nanoparticles)

On March 12 2020, **Medicago** announced the successful production of Virus-Like Particle (VLPs) of SARS-CoV-2 (https://www.medicago.com/en/covid-19-programs/). Preclinical studies were to be initiated in a very short timeframe. A partnership with Glaxo SmithKline allowed combination of the VLPs with an adjuvant (https://www.gsk.com/en-gb/media/press-releases/gsk-and-medicago-announce-collaboration-to-develop-a-novel-adjuvanted-covid-19-candidate-vaccine/). The vaccine candidate is currently being evaluated in a phase 1 staggered dose-escalation clinical trial (https://clinicaltrials.gov/ct2/show/NCT04450004?term=medicago&cond=COVID-19&draw=2&rank=1).

Novavax previously developed vaccine candidates against SARS-CoV and MERS-CoV (see for instance, Coleman Vaccine 2014, see ***below***). Purified full-length MERS and SARS S proteins formed ~25 nm diameter particles consisting of multiple S protein molecules. The antigens were combined with Matrix M1 adjuvant and evaluated in mice. On May 11, the company announced that CEPI will invest up to $384 million of additional funding, on top of $4 million invested in March, to advance clinical development of NVX-CoV2373, Novavax' coronavirus vaccine candidate against SARS-CoV-2. The additional funding from CEPI will also support rapid scale-up of the NVX-CoV2373 vaccine antigen, as well as Novavax' proprietary Matrix-M™ adjuvant, which is expected to enhance immune responses by stimulating high levels of neutralizing antibodies (http://ir.novavax.com/news-releases/news-release-details/novavax-receive-388-million-funding-cepi-covid-19-vaccine). The vaccine candidate is now undergoing phase 1/2 clinical testing in 1419 volunteers in Australia (https://clinicaltrials.gov/ct2/show/NCT04368988?term=covid-19+vaccine&recrs=abdf&draw=2). According to company communication, in the Phase 1 portion of the Phase 1/2 clinical trial, NVX-CoV2373 was generally well-tolerated and elicited robust antibody responses numerically superior to that seen in human convalescent sera (https://ir.novavax.com/news-releases/news-release-details/novavax-initiates-efficacy-trial-covid-19-vaccine-south-africa). A phase 2b as well as a phase 3 trial are now ongoing.

Fusion protein-based approach

Viral fusion proteins undergo structural rearrangements from a metastable pre-fusion conformation to a highly stable post-fusion conformation (https://www.pharmalicensing.com/detail.php?uid=66499). Traditional approaches to recombinant expression of these proteins typically result in premature triggering and a conformational shift to the structurally more stable post-fusion form. The "molecular clamp" approach developed by the University of Queensland, Australia, uses a polypeptide moiety and has been shown to display increased stability over alternate stabilizing trimerization domains (https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018176103). This technique has already been used to produce chimeric polypeptides that mimic the pre-fusion conformations of HIV, respiratory

syncytial virus, influenza, measles and Ebola viruses. The University of Queensland has been requested to use this technology to develop a vaccine candidate against COVID-19 (https://www.uq.edu.au/news/article/2020/01/race-develop-coronavirus-vaccine). A partnership with CSL's influenza vaccines company, Seqirus, supports the rapid development and large-scale manufacture of the vaccine candidate (V451). V451 (formulated with MF59 adjuvant) is currently undergoing phase 1 evaluation (https://clinicaltrials.gov/ct2/show/NCT04495933).

Other subunit candidates

Dai (Cell 2020, see ***below***) described a dimeric form of MERS-CoV RBD that significantly increased neutralizing antibody responses compared to conventional monomeric form and protected mice against MERS-CoV infection. Crystal structure showed RBD-dimer fully exposed dual receptor-binding motifs, the major target for neutralizing antibodies. Structure-guided design further yielded a stable version of RBD-dimer as a tandem repeat single-chain (RBD-sc-dimer) which retained the vaccine potency. This strategy was used to design a vaccine candidate against COVID-19. RBD-sc-dimers in pilot scale production yielded high yields, supporting their scalability. A phase 1 trial evaluates this vaccine candidate in 50 volunteers in China (https://clinicaltrials.gov/ct2/show/NCT04445194).

A team from Flinders University, Oracle Cloud technology and Vaxine Pty Ltd, is developing another subunit vaccine candidate against SARS-CoV-2 (https://news.flinders.edu.au/blog/2020/04/03/flinders-targets-covid-19-vaccine/). The candidate, made of S antigen (25µg) combined to 15 mg Advax-2 adjuvant, is undergoing phase 1 clinical testing in Australia (https://clinicaltrials.gov/ct2/show/NCT04453852?term=vaxine&cond=COVID-19&draw=2&rank=1).

Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd. also has clinical trials ongoing to evaluate a non-adjuvanted subunit vaccine produced in CHO cells (see for instance, https://clinicaltrials.gov/ct2/show/NCT04445194?term=longcom&draw=2&rank=2).

Adjuvanted vaccines

As indicated above (see ***Fusion protein-based approach***), the University of Queensland created a subunit vaccine, which has been formulated with MF59.

Sanofi Pasteur's (formerly Protein Sciences) vaccine candidate is produced by baculovirus expression platform, which was initially developed to manufacture large quantities of pandemic influenza vaccines. A collaboration with GSK allowed for the evaluation in a phase 1/2 clinical trial of 2 different adjuvant formulations of the vaccine candidate (NCT04537208).

Another adjuvanted vaccine candidate is based on the S-trimer subunit vaccine candidate of Clover Biopharmaceuticals Inc (SCB-2019) (https://www.gsk.com/en-gb/media/press-releases/clover-and-gsk-announce-research-collaboration-to-evaluate-coronavirus-covid-19-vaccine-candidate-with-pandemic-adjuvant-system/). A randomized, double blind, placebo controlled, first-in-human study is currently ongoing to assess safety, reactogenicity, and immunogenicity of SCB-2019 either administered alone or with AS03 adjuvant or with CpG 1018 adjuvant plus Alum formulation, in healthy subjects (https://clinicaltrials.gov/ct2/show/NCT04405908?term=antibody&recrs=adefh&type=Intr&cond=COVID-19&draw=1&rank=43).

Vectored vaccines

Adenovirus vectors

The **Ad5-nCoV** vaccine of CanSino Biologics is a replication-defective adenovirus type 5 vector expressing SARS-CoV-2 S protein. Phase 1 and 2 clinical trials were initiated respectively in March and April 2020. The phase 1 trial was a single-centre, open and dose-escalation trial, testing safety and tolerance of Ad5-nCoV in healthy adults, aged 18 to 60 years. The low-, middle- and high-dosage groups sequentially enrolled 36 patients each, who received either

5×10^{10}, 1×10^{11} or 1.5×10^{11} viral particles of Ad5-nCoV (https://clinicaltrials.gov/ct2/show/NCT04313127?term=cansino&cond=covid-19&draw=2&rank=1; http://www.chictr.org.cn/showprojen.aspx?proj=51154). As reported by Zhu (Lancet 2020, see ***below***), at least one adverse reaction within the first 7 days after vaccination was reported in 30 (83%) participants in the low dose group, 30 (83%) participants in the middle dose group, and 27 (75%) participants in the high dose group. The most common injection site adverse reaction was pain, which was reported in 58 (54%) vaccine recipients, and the most commonly reported systematic adverse reactions were fever (50 [46%]), fatigue (47 [44%]), headache (42 [39%]), and muscle pain (18 [17%]. Most adverse reactions that were reported in all dose groups were mild or moderate in severity. No serious adverse event was noted within 28 days post-vaccination. ELISA antibodies and neutralising antibodies increased significantly at day 14, and peaked 28 days post-vaccination. Specific T-cell response were found to peak at day 14 post-vaccination. The phase 2 trial, conducted in a total of 508 volunteers, evaluated only the 2 lower doses of the candidate (Zhu, Guan et al. Lancet 2020, see ***below***). In the 1×10^{11} and 5×10^{10} viral particles dose groups, the RBD-specific ELISA antibodies peaked at 656·5 (95% CI 575·2–749·2) and 571·0 (467·6–697·3), with seroconversion rates at 96% (95% CI 93–98) and 97% (92–99), respectively, at day 28. Both doses of the vaccine induced significant neutralising antibody responses to live SARS-CoV-2, with GMTs of 19·5 (95% CI 16·8–22·7) and 18·3 (14·4–23·3) in participants receiving 1×10^{11} and 5×10^{10} viral particles, respectively. Specific IFN-γ enzyme-linked immunospot assay responses post vaccination were observed in 227 (90%, 95% CI 85–93) of 253 and 113 (88%, 81–92) of 129 participants in the 1×10^{11} and 5×10^{10} viral particles dose groups, respectively. Solicited adverse reactions were reported by 183 (72%) of 253 and 96 (74%) of 129 participants in the 1×10^{11} and 5×10^{10} viral particles dose groups, respectively. Severe adverse reactions were reported by 24 (9%) participants in the 1×10^{11} viral particles dose group and one (1%) participant in the 5×10^{10} viral particles dose group. No serious adverse reactions were documented. On June 25th, China's Central Military Commission approved the use of the vaccine (for military purposes) for one year (https://medicalxpress.com/news/2020-06-chinese-coronavirus-vaccine-military.html).

The Jenner Institute developed a ChAdOx1 COVID-19 candidate, **AZD1222**, based on the non-replicating chimpanzee adenovirus platform, previously used for a vaccine against MERS which was tested in phase 1 trials in UK and KSA (http://www.ox.ac.uk/news/2020-02-07-oxford-team-begin-novel-coronavirus-vaccine-research#). The vaccine candidate was designed to encode a codon-optimised full-length S protein of SARS-CoV-2 (YP_009724390.1) with a human tPA leader sequence. A partnership with Advent in Italy allowed for the manufacturing of clinical batches and initiation of a phase 1/2 study. On April 30, Oxford University announced a partnership with AstraZeneca for the development and potential large-scale distribution of the vaccine candidate (http://www.ox.ac.uk/news/2020-04-30-oxford-university-announces-landmark-partnership-astrazeneca-development-and). Preclinical immunogenicity data following single vaccination with ChAdOx1 nCoV-19by were presented by Van Doremalen (Nature 2020, see ***below***). In rhesus macaques, the vaccine candidate was found to significantly reduce viral load in bronchoalveolar lavage fluid and respiratory tract tissue upon challenge with SARS-CoV-2. However, no difference in viral load in nose swabs was found on any days between vaccinated and control animals. Folegatti reported the outcome of the phase 1/2, single-blind, randomised controlled trial of the vaccine candidate (Lancet 2020, see ***below***). A total of 1077 participants were enrolled and assigned to receive either ChAdOx1 nCoV-19 (n=543) or MenACWY (n=534), ten of whom were enrolled in a non-randomised ChAdOx1 nCoV-19 prime-boost group. Local and systemic reactions were more common in the ChAdOx1 nCoV-19 group and many were reduced by use of prophylactic paracetamol, including pain, feeling feverish, chills, muscle ache, headache, and malaise (all $p<0·05$). There were no serious adverse events related to ChAdOx1 nCoV-19. In the ChAdOx1 nCoV-19 group, S-specific T-cell responses peaked on day 14 (median 856 spot-forming cells per million peripheral blood mononuclear cells, IQR 493–1802; n=43). Anti-S IgG responses rose by day 28 (median 157 ELISA units [EU], 96–317; n=127), and were boosted following a second dose (639 EU, 360–792; n=10). Neutralising antibody responses against SARS-CoV-2 were detected in 32 (91%) of 35 participants after a single dose or in 35 (100%) participants depending on the method used. After a booster dose, all participants had neutralising activity. Neutralising antibody responses correlated strongly with antibody levels measured by ELISA. Phase 2/3 and phase 3 trials of the

candidate vaccine are ongoing (https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001228-32/GB and http://www.isrctn.com/ISRCTN89951424). On September 9 2020, the company announced a voluntary pause of vaccination across all trials to allow for a review of the safety data following a single event of an unexplained illness that occurred in the UK Phase 3 trial (https://www.astrazeneca.com/media-centre/press-releases/2020/statement-on-astrazeneca-oxford-sars-cov-2-vaccine-azd1222-covid-19-vaccine-trials-temporary-pause.html). The trials resumed in the UK on September 12 (https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2020/covid-19-vaccine-azd1222-clinical-trials-resumed-in-the-uk.html), and globally in the following weeks (https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2020/fda-authorises-restart-of-the-covid-19-azd1222-vaccine-us-phase-iii-trial.html). On October 1st, the EMA announced that the committee has started a rolling review of the product, whereby a first batch of non-clinical data on the vaccine is already being reviewed (https://www.ema.europa.eu/en/news/ema-starts-first-rolling-review-covid-19-vaccine-eu).

Russia also conducted a national clinical trial of 2 vaccine candidates developed at the **Gamaleya** Research Institute. The candidates are recombinant adenovirus vectors based on either the human adenovirus type 26 or type 5 virus, containing the SARS-CoV-2 S protein gene (https://www.trialsitenews.com/gamaleya-research-institute-developed-covid-19-vaccine-clinical-trial-commences-across-russia/). Two open trials that enrolled 38 study participants were reported by Logunov (Lancet 2020, see ***below***). All participants produced antibodies to SARS-CoV-2 glycoprotein. Surprisingly, Russia's president Vladimir Putin announced on 11 August that the country's health regulator had become the world's first to approve a CoV vaccine for widespread use. As Russia hadn't completed large trials to test the safety and efficacy of the vaccine, scientists worldwide have condemned the decision as dangerously rushed (Callaway Nature 2020, see ***below***). A large- scale phase 3 trial is now ongoing (NCT04530396).

As early as by the end of January 2020, Johnson & Johnson (Janssen Vaccines & Prevention) announced that it has initiated efforts to develop a vaccine candidate against COVID-19 (https://www.jnj.com/johnson-johnson-launches-multi-pronged-response-to-coronavirus-global-public-health-threat). The vaccine program is leveraging Janssen's AdVac® and PER.C6® technologies that provide the ability to rapidly upscale production of the optimal vaccine candidate. These are the same technologies that were used in the development and manufacturing of an investigational Ebola adenovirus type 26 vector vaccine, which is currently deployed in the Democratic Republic of the Congo and Rwanda. They were also used to construct the Company's Zika, respiratory syncytial virus and HIV vaccine candidates. A randomized, double-blind, placebo-controlled phase 1/2a study in 1045 volunteers to evaluate the safety, reactogenicity, and immunogenicity of the **Ad26COVS1** vaccine candidate in adults aged 18 to 55 years inclusive and adults aged 65 years and older (NCT04436276). A pivotal phase 3 trial is currently ongoing in 60000 participants (ENSEMBLE). On October 23 2020, the company announced that it is preparing to resume recruitment in this phase 3 trial after a temporary pause. After a thorough evaluation of a serious medical event experienced by one study participant, no clear cause has been identified. Based on the information gathered and the input of independent experts, the Company found no evidence that the vaccine candidate caused the event (https://www.jnj.com/our-company/johnson-johnson-prepares-to-resume-phase-3-ensemble-trial-of-its-janssen-covid-19-vaccine-candidate-in-the-us).

On April 23 2020, ReiThera, Leukocare and Univercells announced a strategic collaboration for the development and large-scale manufacturing of a novel adenovirus vector-based vaccine against COVID-19 (https://www.reithera.com/2020/04/23/reithera-leukocare-and-univercells-announce-pan-european-consortium-for-the-fast-track-development-of-a-single-dose-adenovirus-based-covid-19-vaccine/). The Replication defective Simian Adenovirus (**GRAd**) encoding S candidate is used as a single dose vaccine. A phase 1 clinical trial is currently reported as ongoing (EudraCT 2020-002835-31).

According to company communication, Altimmune develops a single-dose intranasal COVID-19 vaccine candidate, based on the technology used for their influenza vaccine candidate, **NasoVAX**, which is known to induce mucosal

immunity as well as cell and IgG responses (https://ir.altimmune.com/static-files/f9e406df-9cc0-4fb7-9d9c-52d780679780). The candidate is a replication-deficient adenovirus 5 vector expressing SARS-CoV-2 S protein.

Modified Vaccinia Ankara vector

GeoVax Labs, Inc., together with BravoVax, a vaccine developer in Wuhan, China, today announced the signing of a Letter of Intent to jointly develop a vaccine against COVID-19. Under the collaboration, GeoVax will use its MVA-VLP vaccine platform and expertise to design and construct the vaccine candidate using genetic sequences from the ongoing coronavirus outbreak. BravoVax will provide further development, including testing and manufacturing support, as well as direct interactions with Chinese public health and regulatory authorities. (https://www.geovax.com/news/geovax-and-bravovax-wuhan-china-to-collaborate-on-development-of-coronavirus-vaccine).

Other vectors

Tonix Pharmaceuticals announced a strategic collaboration with Southern Research to support the development of a vaccine, TNX-1800*, which is a live modified horsepox virus vaccine for percutaneous administration, to protect against COVID-19 (https://www.tonixpharma.com/news-events/press-releases/detail/1191/tonix-pharmaceuticals-announces-research-collaboration-with).

Inactivated vaccines

Several inactivated vaccine candidates have been described and are currently evaluated in clinical trials.

Sinovac Biotech used a similar strategy as selected for a SARS vaccine tested in a clinical trial 16 years ago (Cohen Science 2020, see ***below***). The SARS-CoV-2 vaccine candidate (PiCoVacc) is made by chemically inactivating whole virus particles and combination to Alum adjuvant. As reported by Gao, Bao et al. (Science 2020, see ***below***) the vaccine induced potent neutralizing responses in various animal models. Immunization with two different doses (3 µg or 6 µg per dose) provided partial or complete protection in rhesus macaques against SARS-CoV-2 challenge. A publication by Risson (Nat Rev Imm 2020, see ***below***) commenting these data highlighted the expected scalability of the inactivation method (β-propiolactone). The vaccine entered phase 3 clinical evaluation in July (https://clinicaltrials.gov/ct2/show/NCT04456595).

Clinical development of other inactivated vaccine candidates produced in Vero cells, led by the Beijing and Wuhan Institutes of Biological Products and Sinopharm, have also been reported as reaching phase 3 (http://www.chictr.org.cn/showprojen.aspx?proj=56651). Wang, Zhang, Huang et al. (Cell 2020, see ***below***) reported the pilot-scale production of this inactivated SARS-CoV-2 vaccine candidate (BBIBP-CorV) that induces high levels of neutralizing antibodies titers in mice, rats, guinea pigs, rabbits, and nonhuman primates (cynomolgus monkeys and rhesus macaques). Two-dose immunizations using 2 mg/dose were shown to provide highly efficient protection against SARS-CoV-2 intratracheal challenge in rhesus macaques. Xia subsequently presented an interim analysis of a randomized phase 1/2 placebo-controlled trials of the vaccine (ChiCTR2000031809, JAMA 2020, see ***below***). In 96 healthy adults randomized to aluminum hydroxide (alum) only and low, medium, and high vaccine doses on days 0, 28, and 56, 7-day adverse reactions occurred in 12.5%, 20.8%, 16.7%, and 25.0%, respectively; geometric mean titers of neutralizing antibodies at day 14 after the third injection were 316, 206 and 297 in the low-, medium-, and high-dose groups, respectively. In 224 healthy adults randomized to the medium dose, 7-day adverse reactions occurred in 6.0% and 14.3% of the participants who received injections on days 0 and 14 vs alum only, and 19.0% and 17.9% who received injections on days 0 and 21 vs alum only, respectively; geometric mean titers of neutralizing antibodies in the vaccine groups at day 14 after the second injection were 121 vs 247, respectively.

COVAXIN (or BBV152), a COVID-19 vaccine candidate by Bharat Biotech is developed in collaboration with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV). This vaccine received approval for Phase 1

and 2 human clinical trials and the trials commenced in July, 2020. After successful completion of the interim analysis from these clinical trials, Bharat Biotech received DCGI approval for Phase 3 clinical trials in 26 000 participants in over 25 centres across India (https://www.bharatbiotech.com/covaxin.html).

Live-attenuated vaccines

Codagenix announced a collaboration with the Serum Institute of India to rapidly co-develop a live-attenuated vaccine against COVID-19 (https://www.prnewswire.com/news-releases/codagenix-and-serum-institute-of-india-initiate-co-development-of-a-scalable-live-attenuated-vaccine-against-the-2019-novel-coronavirus-covid-19-301004654.html). Codagenix uses viral deoptimization to synthesize "rationally designed," live-attenuated vaccines. According to another announcement of the company dated September 22 2020, Serum Institute of India has initiated manufacturing of Codagenix's intranasal live-attenuated COVID-19 vaccine candidate (https://www.prnewswire.com/news-releases/serum-institute-of-india-initiates-manufacturing-of-codagenixs-intranasal-live-attenuated-covid-19-vaccine-candidate-301135221.html?tc=eml_cleartime).

Other approaches

Symvivo's bacTRL platform is an orally administered, genetically modified probiotic bacteria which colonizes the gut, binds directly to intestinal epithelial cells and constitutively replicates, secretes and delivers plasmid DNA molecules encoding antigenic transgenes and neutralizing nanobodies (https://www.symvivo.com/covid-19). A phase 1 clinical trial is ongoing to evaluate bacTRL-Spike administered orally (NCT04334980). The S protein has also been combined to N protein and M glycoprotein for a trivalent vaccine called bacTRL-Tri.

The Shenzhen Geno-immune Medical Institute reported 2 phase 1 clinical trials evaluating cell-based approaches of vaccination against COVID-19. The first one investigated a lentiviral vector system (NHP/TYF) to express viral proteins and immune modulatory genes to modify dendritic cells (DCs) and thereby activate T cells. The vaccine candidate (LV-SMENP) uses a COVID-19 minigene engineered based on multiple viral genes (https://clinicaltrials.gov/ct2/show/NCT04276896?term=covid-19+vaccine&recrs=adf&draw=2&rank=6). The second trial investigates artificial antigen presenting cells (aAPC) modified by the lentiviral vector system to express viral proteins (minigene based on conserved domains of the viral structural proteins and a polyprotein protease) and immune modulatory genes (https://clinicaltrials.gov/ct2/show/NCT04299724?term=covid-19+vaccine&recrs=adf&draw=2&rank=4).

Aivita Biomedical, Inc also plans an adaptive phase 1b/2 randomized clinical trial of a preventive vaccine candidate (AV-COVID-19) made of autologous DCs loaded with SARS-CoV-2 antigens, with or without GM-CSF. The trial is to enrol a total of 180 study participants (https://clinicaltrials.gov/ct2/show/NCT04386252).

A therapeutic vaccine approach has been proposed by Immunitor. The V-SARS candidate said to be made from heat-inactivated plasma from COVID-19 donors, and administered once-daily as an oral pill (https://clinicaltrials.gov/ct2/show/NCT04380532?term=covid-19+vaccine&recrs=abdf&draw=2&rank=16). However, while technical details have not been disclosed, it is unclear that this candidate can be considered as a real vaccine. A phase 1/2 clinical trial is reported as currently ongoing in 20 patients.

Planning vaccine access

To break the current epidemic, epidemiologists have suggested that 70% of the population may need to develop immunity. As of today, only a minor fraction of the population has been found to display antibodies against SARS-CoV-2 (see ***Seroepidemiology***). Vaccines are therefore perceived as the best way of rapidly inducing herd immunity. However, as reported by Cornwall, polls have found as few as 50% of people in the United States are committed to receiving a vaccine, with another quarter wavering (https://www.sciencemag.org/news/2020/06/just-50-americans-plan-get-covid-19-vaccine-here-s-how-win-over-rest). Some of the communities most at risk from the virus are also

the most leery: among Black people, who account for nearly one-quarter of U.S. COVID-19 deaths, 40% said they wouldn't get a vaccine in a mid-May poll by the Associated Press and the University of Chicago. In France, according to Cornwall, 26% said they wouldn't get a coronavirus vaccine. However, a European survey by Neumann-Böhme (Eur J Health Eco, see ***below***) rather suggested that France has the largest group of people who are unsure about getting vaccinated (28%) while 10% are opposed to a COVID-19 vaccination. Overall, 73.9% of the 7664 participants from Denmark, France, Germany, Italy, Portugal, the Netherlands, and the UK stated that they would be willing to get vaccinated against COVID-19 if a vaccine would be available. A further 18.9% of respondents stated that they were not sure, and 7.2% stated that they do not want to get vaccinated.

Nevertheless, a number of high income countries (such as the UK and the US) have pre-ordered vast amounts of candidate COVID-19 vaccines ahead of their regulatory approval (see for instance Torjesen BMJ 2020: https://www.bmj.com/content/370/bmj.m3226).

However, new vaccines will initially be supply-constrained, requiring a sequential allocation as supply increases to achieve the best public health impact. WHO indicated that equitable distribution is particularly important in the area of vaccines. Therefore, WHO advises that once a vaccine is shown to be safe and effective, and authorized for use, all countries receive doses in proportion to their population size, albeit initially in reduced quantities. This will enable every country to start by immunizing the highest priority populations. (https://www.who.int/publications/m/item/fair-allocation-mechanism-for-covid-19-vaccines-through-the-covax-facility). The selection of target groups according to strategy and policy recommendations is considered of cardinal importance. For example, if the goal is to reduce mortality, those at the highest risk of dying should be prioritized for vaccination, and therapeutics may be reserved for potentially severe cases of illness. Similarly, rapid diagnostic tests and vaccines may be prioritized for essential workers in a scenario where the preservation of essential services is critical.

Seventy-five countries have submitted expressions of interest to the COVAX Facility, a mechanism designed to guarantee rapid, fair and equitable access to COVID-19 vaccines worldwide (https://www.who.int/news-room/detail/15-07-2020-more-than-150-countries-engaged-in-covid-19-vaccine-global-access-facility). The goal of COVAX is by the end of 2021 to deliver two billion doses of safe, effective vaccines that have passed regulatory approval and/or WHO prequalification. These vaccines will be delivered equally to all participating countries, proportional to their populations, initially prioritising healthcare workers then expanding to cover 20% of the population of participating countries. The 75 countries, which would finance the vaccines from their own public finance budgets, partner with up to 90 lower-income countries that could be supported through voluntary donations to Gavi's COVAX Advance Market Commitment (AMC).

Non-vaccine approaches to better host resistance

Host resistance to viral infections can be increased in multiple ways. While more data are still required in the context of COVID-19, there is already sufficient evidence available to support further investigations in this area.

Traditional Chinese Medicine

In China, the use of Traditional Chinese Medicine (TCM) to prevent epidemics of infectious diseases was traced back to ancient Chinese practice cited in Huangdi's Internal Classic (Huang Di Nei Jing), which was written about 2000 years ago (Luo Chin J Integr Med 2020, see ***below***). It suggested two aspects which should be employed to prevent the spread of epidemics. One was to maintain and improve the healthy qi (energy) in the body by taking preventive medicine (Xiaojin dan, the first recommended formula of TCM to prevent pestilence), healthy diet care, exercise and so on, so as to resist the invasion of external pathogen, and the other was to avoid the source of infection. These two principles of epidemic disease prevention have been followed by TCM practitioners until now.

Chinese medical classics also described the basic nature of the current pandemic disease millennia ago. The Yellow Emperor's Classic states: "When two types of deficiency encounter each other they will pathologically effect the body". One is the external type, corresponding to abnormal climate conditions create the external terrain for the development of an epidemic. The climate was unusual in Wuhan with its continuous rain and abnormal warmth during the winter, which affect the body with dampness and impaired qi, especially in the lung and the spleen (Sun J Chin Med 2020, see ***below***). Dampness is at the core of COVID-19, characterized by a sticky coating on the tongue and a slippery pulse corresponding to turbid damp obstructing the lung. Besides, if the body presents some internal deficiency that impairs its ability to defend itself, this external condition could favour manifestations of the disease. In addition to these two deficiency factors, the Classic speaks about "invasion into the body", by an epidemic toxin (yidu) as another prerequisite for epidemic development. The epidemic toxins (SARS-Cov2) can only invade the body when its defences have become compromised. Besides, a patient's emotional state influences the onset and development of the disease. The Chinese medical classics say that the Heart is the sovereign of the organ systems, and "When the sovereign is clear and bright, all below is at peace; when the sovereign is not clear and bright, all of the other organs are at peril." Most diseases invade the body layers by layers, from the surface of the body (the three yang channels) and then progress deeper inside (the three yin channels). SARS-CoV-2 typically invades several channels simultaneously, and right from the start. This is the reason why many patients exhibit symptoms from different organ systems (respiratory symptoms, digestive problems or neurological symptoms). Acupuncture and medicinal herbs must evade epidemic toxins from the affected yang channels, then it won't be able to go any deeper into the yin channels, and then won't impair vital organs (e.g. kidney) (Liu, Report from the Front Line in Wuhan, Classical Chinese Medicine, available at https://classicalchinesemedicine.org/report-from-front-line-wuhan/?fbclid=IwAR2vXVOkJpL5kOlUmKrkEQGAEMFJSzsbQgydh9ScfB6IGnBg8X-BA8LJYpE). Several stages of COVID-19 were described according to invaded channels with corresponding impaired organs. For each stage, specific medicinal herbs and acupuncture protocols are described (Wang, Expert Consensus Statement on the Prevention, Diagnosis and Treatment of COVID-19 Infection in Children, Chinese Archives for Traditional Chinese Medicine, available at https://classicalchinesemedicine.org/expert-consensus-statement-on-the-prevention-diagnosis-and-treatment-of-covid-19-infection-in-children/).

Ayurveda

Ayurveda, a traditional system of medicine, originated in India more than 3,000 years ago. The term Ayurveda is derived from the Sanskrit words ayur (life) and veda (science or knowledge) (Golechha Brain Behav Imm 2020, see ***below***). The classic Ayurveda text Charaka Samhita, mentioned about epidemic management and defines immunity as the ability to prevent and arrest the progression of disease for maintaining homeostasis. The Ayurveda pays larger emphasis on building strength of mind and body to cope with various stressors, including infection. Similar to innate and acquired immunity, the Ayurveda concept of immunity (Bala or strength) is classified as natural (Sahaja), chronobiologic (Kalaja), and acquired (Yuktikrut). In Ayurveda several treatment options are available for enhancing immunity against respiratory illnesses, these include certain immunomodulators (known as Rasayana), local and systemic interventions. Local prophylaxis measures such as herbal decoctions, consumptions of hot water, gargling with medicated water, and steam inhalation are described in Ayurveda for respiratory illnesses.

In India, several initiatives have been taken to utilise the vast potential of Ayurveda in this pandemic. The Ministry of Ayush, a nodal Ministry of Complementary and Alternative Medicine, has released a set of guidelines for boosting immunity and measures for self-care by using Ayurvedic principles. Gujarat, one of the western states of India, has initiated a study, in which Ayush treatment will be administered to asymptomatic patients of COVID-19 and the state government has also distributed ayurvedic medicines to millions of citizens for boosting their immunity against COVID-19. The Kerala, southern Indian state, also started use of Ayurveda in mitigating the spread of COVID-19. The government has categorised the population in seven categories based on the possible spread of the virus, and Ayurvedic treatment has been advised accordingly.

Psychoneuroimmunity aspects

A view point by Kim (Brain Behav Imm 2020, see ***below***) provided a reminder of the impact of a healthy lifestyle, regular exercise, balanced nutrition, quality sleep and a strong connection with people on resistance to infections. Although the psychological impact of COVID-19 remains unclear, infected patients may experience anxiety, depression, guilt, stigma, and anger. Such emotional issues may reduce immunity and compromise recovery. Current prevention efforts are largely focused on social distancing. The authors suggested that all forms of psychological support should be routinely implemented not only for psychological resilience, but also to enhance immunity against COVID-19. A letter to the Editor by Lazzari (Brain Behav Imm 2020, see ***below***) further advised in favor of a large-scale integration of medicine and psychology.

Of interest, Burtscher (Scand J Med Sci Sports 2020, see ***below***) noted that isolation of individuals in combination with fear of contagion, quarantine and stigma, as well as with potential (mis)information overload causes chronic stress and is associated with a burden on mental health, posing risk factors for anxiety and depression. It is well understood that chronic stress is a major modulator of immunity and thus directly influences the probability of infection.

BCG vaccination

The BCG vaccine has beneficial nonspecific (off-target) effects on the immune system that protect against a wide range of other infections. O'Neill (Nat Rev Immunol 2020, see ***below***) discussed the non-specific beneficial effects of BCG against viral infections and provided a background to support the contention that vaccine may afford protection to COVID-19. Curtis (Lancet 2020, see ***below***) indicated that randomised controlled trials are underway in the Netherlands and Australia to assess whether prophylactic administration of BCG-Danish reduces the incidence and severity of COVID-19 in health-care workers, and the effect this has on time away from work (respectively, NCT04328441 in 1500 volunteers and NCT04327206 in 10 078 volunteers). By October 20 2020, 8 additional trials of BCG vaccination to assess protection against COVID-19 were reported as ongoing in the Netherlands (NCT04417335, N=2014 volunteers from 60 years of age ; NCT04537663, N=5200), U.S.A. (NCT04348370, N=1800), South Africa (NCT04379336, N=500), Greece (NCT04414267, N=900), France (NCT04384549, N=1120), India (NCT04475302, N=2175) and Mexico (NCT04461379, N=908). Additional phase 3 clinical trials evaluate the VPN1002 tuberculosis vaccine candidate for its efficacy at preventing COVID-19 (NCT04387409, NCT04435379 and NCT04439045). VPN1002 is a recombinant BCG which expresses listeriolysin from *Listeria monocytogenes* and is devoid of urease C (Kaufmann Front Imm 2020, see ***below***). Development of this tuberculosis vaccine candidate started in the 1990s and is still ongoing. BCG vaccination is also evaluated in a therapeutic approach (NCT04369794 in Brazil).

As reviewed by Kamat (Front Pharm, see ***below***), some statistical data depicted a higher death rate of COVID-19 in non-BCG vaccinated countries than in BCG-vaccinated nations. However, in view of the high death rate for patients over 70 years of age, and given the fact that BCG vaccination is typically given early in life, Wassenaar (Lett Appl Microb 2020, see ***below***) compared countries that had introduced BCG in the 1950s with those that had not. No effect on COVID-19 case fatality rate or number of deaths per population could be demonstrated.

In conclusion, BCG vaccines provide trained and heterologous immunity against multiple diseases by eliciting non-specific innate and adaptive immunities. However, it is too early to conclude on a role of BCG vaccination on COVID-19 without randomized clinical trials data and further scientific research. As of today, the WHO does not recommend BCG vaccination for COVID-19 prevention.

Manipulating the commensal microbiota

A plethora of evidence suggests that the commensal microbiota regulates and is in turn regulated by invading viruses through diverse mechanisms, thereby having stimulatory or suppressive roles in viral infections (reviewed by Li Front Imm 2019, see ***below***; Baud Front Publ Health 2020, see ***below***). Such knowledge could help design alternative approaches to the control of a number of viral infections, including COVID-19. A trial investigating the underlying

mechanism of development of lower respiratory tract infection (LRTI) after viral infection showed for instance that patients with a higher abundance of butyrate-producing bacteria in their faecal samples had a 5-fold lower possibility of developing viral LRTI. Considering that butyrate-producing bacteria are favoured by a diet rich in fibers, similar studies on COVID-19 appear useful to undertake.

A particular strain of *Streptococcus salivarius*, known as K12, has been clinically demonstrated to help create a stable upper respiratory tract microbiota capable of protecting the host from pathogenic bacteria, fungi and viruses (Di Pierro Minerva Med 2020, see ***below***). The proposed antiviral effect has been attributed to an adaptive immune response as revealed by detection of enhanced levels of IFN-γ in human saliva 10 hours after oral administration, with values at 24 hours between 22 and 139 pg/ml. IFN-γ release occurs without modifying either IL-1β or TNF-α levels, and substantially lowering IL-8 release, therefore occurring without evoking an inflammatory response. Moreover, ***Streptococcus salivarius* K12** is capable of suppressing bronchial inflammatory responses by inhibiting NF-κB pathways and other important human immune cell functions. Interestingly, the authors noted that a significant difference in the lung microbiota composition has previously been reported between patients with SARS-CoV-2 pneumonia and healthy subjects (Shen Clin Inf Dis 2020, see ***below***). Among 8 subjects with SARS-CoV-2 pneumonia, 6 had a pathogen-enriched microbiota, and the other two had a commensal-enriched microbiota.

d'Ettorre (Front Med 2020, see ***below***) reported the outcome of a clinical study in 70 patients positive for COVID-19, where a specific bacterial formulation showed a significant ameliorating impact on the clinical conditions of patients. Forty-two patients received hydroxychloroquine, antibiotics, and tocilizumab, alone or in combination. A second group of 28 subjects received the same therapy added with oral bacteriotherapy, using a multistrain formulation. The formulation administered in this study, Sivomixx® (SivoBiome® in USA), contained: *Streptococcus thermophilus* DSM 32345, *L.acidophilus* DSM 32241, *L. helveticus* DSM 32242, *L. paracasei* DSM 32243, *L. plantarum* DSM 32244, *L. brevis* DSM 27961, *B. lactis* DSM 32246, *B. lactis* DSM 32247. The oral bacteriotherapy involved the use of 2400 billion bacteria per day. The two cohorts of patients were comparable for age, sex, laboratory values, concomitant pathologies, and the modality of oxygen support. Within 72 h, nearly all patients treated with bacteriotherapy showed remission of diarrhoea and other symptoms as compared to less than half of the not supplemented group. The estimated risk of developing respiratory failure was eight-fold lower in patients receiving oral bacteriotherapy. Both the prevalence of patients transferred to ICU and mortality were higher among the patients not treated with oral bacteriotherapy.

Vitamins and nutrition

Calder (Nutrients 2020, see ***below***) noted that a wealth of mechanistic and clinical data show that vitamins, including vitamins A, B6, B12, C, D, E, and folate; trace elements, including zinc, iron, selenium, magnesium, and copper; and the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid play important and complementary roles in supporting the immune system. Inadequate intake and status of these nutrients are widespread, leading to a decrease in resistance to infections. The authors encourage public health officials to include nutritional strategies in their recommendations to improve public health. The authors did not indicate if any research is ongoing on the impact of diet on COVID-19, but a review by Briguglio (Front Med 2020, see ***below***) noted that a greater understanding of the link between nutrition and SARS-CoV-2 is needed.

Shi (Cell Death Diff 2020, see ***below***) indicated that **vitamin B3** has a protective role on lung tissue damage, and suggested its use as soon as cough is observed.

Grant (Nutrients 2020, see ***below***) presented evidence that **vitamin D** supplementation could reduce the risk of COVID-19 infections and deaths. This evidence includes that the outbreak occurred in winter, a time when 25-hydroxyvitamin D (25(OH)D) concentrations are lowest; that the number of cases in the Southern Hemisphere near the end of summer were low; that vitamin D deficiency has been found to contribute to acute respiratory distress syndrome; and that

case-fatality rates increase with age and with chronic disease comorbidity, both of which are associated with lower 25(OH)D concentration. D'Avolio (Nutrients 2020, see ***below***) retrospectively investigated the 25(OH)D concentrations in plasma obtained from a cohort of patients from Switzerland. In this cohort, significantly lower 25(OH)D levels (p = 0.004) were found in PCR-positive for SARS-CoV-2 (median value 11.1 ng/mL) patients compared with negative patients (24.6 ng/mL); this was also confirmed by stratifying patients according to age >70 years. A recommendation in favour of vitamin D supplementation was also made by McCartney (Ir Med J. 2020, see ***below***). On October 14 2020, a search on Clintrials.gov identified several ongoing studies evaluating vitamin D supplementation used either prophylactically (e.g. NCT04482673, NCT04535791) or therapeutically (e.g. NCT04449718, NCT04552951, NCT04411446).

Curcumin

Curcumin is considered as the major active compound in the rhizome of turmeric (*Curcuma longa*). Curcumin has been used extensively in Ayurveda, Siddha medicine and traditional Chinese medicine for centuries, as it has been associated with a variety of therapeutic properties including antioxidant, analgesic, anti-inflammatory, antiseptic activity, and anti-carcinogenic activity (reviewed by Mathew J Funct Foods 2018, see ***below***). Curcumin's antiviral effects were observed against numerous viruses including parainfluenza virus type 3, vesicular stomatitis virus (VSV), herpes simplex virus, and RSV. Curcumin also appeared as a potent inhibitor when tested for its *in vitro* activity against SARS-CoV on Vero E6 cells (Wen J Med Chem 2007, see ***below***).

A study using an *in silico* approach involving docking and stimulation, demonstrated the dual binding affinity of polyphenolic compounds in which both the viral S protein and ACE2 binds to curcumin (Manoharan Ind J Clin Bioch 2020, see ***below***). Binding of curcumin to receptor-binding domain (RBD) site of viral S protein and also to the viral attachment sites of ACE2 receptor, demonstrated that curcumin can act as potential inhibitory agent antagonizing the entry of SARS-CoV2 viral protein. Moreover, emulsion form of topical application of curcumin may effectively prevent the SARS-CoV2 infection in humans, as the viral entry site of ACE2 receptor is predominantly distributed at the nasal cells, mucosal surface of respiratory tract and eyes.

Further, curcumin has been extensively studied for its role in the regulation of RAAS (renin-angiotensin-aldosterone system) components through which it is known to exert anti-oxidant, anti-inflammatory and antihypertensive effects. Animal studies have implicated the role of curcumin in the downregulation of ACE and AT1R receptor expression in brain tissue and vascular smooth muscle cells, respectively resulting inhibition of Angiotensin II-AT1R mediated effects of hypertension and oxidative stress in animals. Previous studies revealed high level of AT2R and ACE2 expression in myocardial cells treated with curcumin thus exhibiting the protective mechanism of curcumin via modulation of effects mediated by Angiotensin II receptors AT1R and AT2R. Upregulation of AT2R induces suppression of AT1R expression leading to Angiotensin II-AT2R mediated anti-inflammatory effects involving an inhibition of NF-κB activity and oxidative stress. Hence, treatment with curcumin attenuated the proinflammatory effects induced by Angiotensin II-AT1R axis leading to significant decrease in the level of proinfammatory cytokines TNF-α, IL-6 and reactive oxygen species.

Various clinical trials provided promising results suggesting a low toxicity of curcumin. However, many questions and challenges still exist. Curcumin has been reported as an unstable, reactive, non-bioavailable compound (Nelson J Med Chem 2017, see ***below***), and the lack of placebo-controlled trials to support its efficacy in humans has been pointed out (Nelson ACS Med Chem Lett 2017, see ***below***). The distinction between turmeric (the plant), curcuminoids (contained in turmeric and in extracts of turmeric) and curcumin also needs to be highlighted. Curcuminoids, as typically available commercially, contain not only curcumin but three primary components and approximately 15% of oleoresins and essential oil.

Nevertheless, various authors have suggested the use of curcumin as a preventive measure in the inhibition of transmission of SARS-COV2 infection among humans (Gupta Clin Exp Derm, see ***below***; Manoharan Ind J Clin Bioch 2020, see ***below***). An ongoing clinical trial evaluates a spray preparation of ArtemiC, comprising Artemisinin, Curcumin, Boswellia, and Vitamin C in a nanoparticular formulation for COVID-19 therapy (https://clinicaltrials.gov/ct2/show/NCT04382040?term=curcumin&cond=COVID-19&draw=2&rank=1).

Vector control and disease control in animals

Available evidence on SARS-CoV-2 and previous experience with other coronavirus (MERS-CoV and SARS-CoV) and other respiratory viruses (e.g., avian influenza) suggest that there may be zoonotic transmission associated with SARS-CoV-2. The following recommendations were therefore issued by WHO on March 26 2020 (https://www.who.int/health-topics/coronavirus/who-recommendations-to-reduce-risk-of-transmission-of-emerging-pathogens-from-animals-to-humans-in-live-animal-markets). These recommendations may appear as very general, as the animal species that may be involved in such transmission remained largely unknown at that time.

As a general precaution, general hygiene measures are recommended to anyone visiting live animal markets, wet markets or animal product markets. These include regular hand washing with soap and potable water after touching animals and animal products, avoiding touching eyes, nose or mouth with hands, and avoiding contact with sick animals or spoiled animal products. It is also recommended to avoid contact with other animals possibly living in the market (e.g., stray cats and dogs) and with potentially contaminated animal waste or fluids on the soil or structures of shops and market facilities. A last recommendation is to avoid consumption of raw or undercooked animal products.

People with underlying medical conditions are considered at higher risk of severe disease. Therefore, individuals with these underlying medical conditions are recommended to avoid contact with live animal markets, stray animals and wild animals, and should not eat animal raw meat.

Good personal hygiene is specifically recommended to slaughterhouse workers, veterinarians in charge of animal and food inspection in markets, market workers, and those handling live animals and animal products. Use of protective gowns, gloves, masks as well as frequent disinfection of equipment and working stations, is also recommended.

Social interventions

Psychological intervention for affected people

It has been claimed that the mental health needs of patients with confirmed COVID-19, patients with suspected infection, quarantined family members, and medical personnel have been poorly handled in China, and that the organisation and management models for psychological interventions must be improved (Duan Lancet Psych 2020, see ***below***). With disease progression, clinical symptoms become severe and psychological problems in infected patients change; therefore, psychological intervention measures should be targeted and adapted as appropriate. Studies have confirmed that individuals who have experienced public health emergencies still have varying degrees of stress disorders, even after the event is over, or they have been cured and discharged from hospital, indicating these individuals should not be ignored. It is recommended that interventions are based on a comprehensive assessment of risk factors leading to psychological issues, including poor mental health before a crisis, bereavement, injury to self or family members, life-threatening circumstances, panic, separation from family and low household income.

Numerous studies assessed the impact of social isolation and loneliness on the mental health of previously healthy people. A review by Brooks (Lancet 2020, see ***below***) reported negative psychological effects of quarantine, including post-traumatic stress symptoms, confusion, and anger. Stressors included longer quarantine duration, infection fears,

frustration, boredom, inadequate supplies, inadequate information, financial loss, and stigma. In situations where quarantine is deemed necessary, the author recommended officials to quarantine individuals for no longer than required, provide clear rationale for quarantine and information about protocols, and ensure sufficient supplies are provided. Appeals to altruism by reminding the public about the benefits of quarantine to wider society are presented as favourable.

Fitzpatrick (Psychol Trauma 2020, see https://psycnet.apa.org/fulltext/2020-38568-001.html) reported data from a nationally representative sample of 10 368 U.S. adults surveyed during the week of March 23, 2020. Respondents were fearful, averaging a score of nearly 7 on a scale of 10 when asked how fearful they were of COVID-19. Preliminary analysis suggested clear spatial diffusion of COVID-19 fear. Fear appeared to be concentrated in regions with the highest reported COVID-19 cases. Significant differences across several U.S. census regions were noted ($p < .01$). Additionally, significant bivariate relationships were found between socially vulnerable respondents (female, Asians, Hispanic, foreign-born, families with children) and fear, as well as with mental health consequences (anxiety and depressive symptoms).

A rapid review by Loades (J Am Acad Child Adolesc Psychiatry 2020, see ***below***) showed that children and adolescents are probably more likely to experience high rates of depression and probably anxiety during and after enforced isolation ends. This may increase as enforced isolation continues. The authors concluded that clinical services should offer preventative support and early intervention where possible and be prepared for an increase in mental health problems.

Interestingly, a review by Bzdok (Trends Cognitive Sci 2020: see ***below***) noted that we never experienced social isolation before on such a massive scale as we have in response to COVID-19. However, the authors showed that from babies to the elderly, psychosocial embedding in interpersonal relationships is critical for survival. They highlighted the neurocognitive basis of social isolation and its deep consequences not only for mental, but also for physical health.

Social media and information to the general public

Using data collected during the 2015 Middle East Respiratory Syndrome coronavirus (MERS-CoV) outbreak in South Korea, a study reported by Oh (Health Comm 2020, see ***below***) explored the relationships among social media use, risk perception, and preventive behaviours by examining the mediating role of two self-relevant emotions: fear and anger. The findings demonstrate that social media use is positively related to both of these emotions, which are also positively related to the public's risk perception. The findings also indicate that social media use can significantly increase preventive behaviours via the two self-relevant emotions and the public's risk perception.

In China, the government strives to improve the public's awareness of prevention and intervention strategies by providing daily updates about surveillance and active cases on websites and social media (Bao Lancet 2020, see ***below***). Increasingly, psychologists and psychiatrists use the internet and social media (e.g., WeChat, Weibo, etc) to share strategies for dealing with psychological stress. For example, experts from Peking University Sixth Hospital made six suggestions for the public to cope with mental stress. These included assessing the accuracy of information disclosed, enhancing social support systems (e.g., families and friends), eliminating stigma associated with the epidemic, maintaining a normal life under safe conditions, and using the psychosocial service system, particularly telephone-based and internet-based counselling for health-care staff, patients, family members, and the public. Liu (Lancet Psych 2020, see ***below***) even reported that several artificial intelligence (AI) programmes have been put in use as interventions for psychological crises during the epidemic. For example, individuals at risk of suicide can be recognised by the AI programme Tree Holes Rescue,5 by monitoring and analysing messages posted on Weibo, and alerting designated volunteers to act accordingly.

Outside China, at the start of the epidemic, the emergence of misinformation and racism against patients and Chinese visitors has been reported (Shimizu Lancet 2020, see ***below***). Excess demand for surgical masks among the general public also became a serious concern, as it lowered provision for medical facilities including emergency and critical care centres. It has been recommended that mass media take responsibility for providing correct information and creating comprehension among citizens. Effective communication may contribute to lessening the risk for inappropriate behaviour, such as unnecessary visits to health-care facilities, as well as help eliminate fake news and discrimination against patients and Chinese visitors.

However, just as the coronavirus itself, misinformation has spread far and wide, drowning out credible sources of information (Mian BMC Med 2020, see ***below***). Over the last couple of months, posts from the WHO and the US CDC have cumulatively only achieved several hundred thousand engagements, considerably eclipsed by hoax and conspiracy theory sites, which have amassed over 52 million. This serves to emphasise the popularity of unverified sources of information.

Gonçalves-Sá (Nat Med 2020, see ***below***) also highlighted the staggering amount of misinformation propagating online on the topic of COVID-19, including the most concerning conspiracy theory circulating online related to the factitious claim that the virus was engineered by the Chinese, with political or economic goals. The author noted that the decision to delete this misinformation publicly might reinforce conspiracy theories. As an alternative, it was suggested that social-media platforms could attempt to implement simple nudges: asking people whether they are sure they want to share something could activate their best judgment and reduce over-confidence; and introducing time delays on the publication of dubious information, while it is being checked, could slow the spreading process and eventually prevent its publication.

Mian (BMC Med 2020, see ***below***) noted that the disconnect between scientific consensus and members of the public has progressively worsened as society has become further divided in the political climate of today. On February 19 2020, Calisher (Lancet 2020, see https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30418-9/fulltext) published a statement of solidarity to fight against COVID-19 and to promote scientific evidence and unity over misinformation and conjecture.

In February 2020, the Finnish Institute for Health and Welfare started collecting weekly qualitative data on COVID-19 risk perception. The process is based on thematic analysis of emails and social media messages from the public and identifies factors linked to appraisal of risk magnitude, which are developed into risk communication recommendations together with health and communication experts (Lohiniva EuroSurv 2020, see ***below***). The findings were related to five risk perception domains: catastrophic potential (e.g. emotional response, anticipation of growth of the epidemic), probability of dying (death perceived as likely), reasons for exposure (e.g. contact with infected persons, people coming from abroad or foreign nationals), the belief of being in control of the situation (a lack of the belief that a person can individually control the spread of the epidemic and instead a strong belief that authorities can do that), and trust towards authorities (distrust of information provided and actions taken by the authorities). This process helped develop context-specific risk communication messages.

Mental support for health care workers

Several reports described the importance of maintaining staff mental health when dealing with the epidemic. For instance, Tan (Ann Int Med 2020, see ***below***) reported the outcome of a study where, from 19 February to 13 March 2020, health care workers who were caring for patients with COVID-19 at 2 major tertiary institutions in Singapore answered a self-administered questionnaire. Sixty-eight (14.5%) participants screened positive for anxiety, 42 (8.9%) for depression, 31 (6.6%) for stress, and 36 (7.7%) for clinical concern of posttraumatic stress disorder. The prevalence of anxiety was higher among nonmedical health care workers than medical personnel (20.7% versus 10.8%; adjusted

prevalence ratio, 1.85 [95% CI, 1.15 to 2.99]; P = 0.011), after adjustment for age, sex, ethnicity, marital status, survey completion date, and presence of comorbid conditions.

Various measures of psychological intervention were reported (see for instance Chen Lancet Psych 2020, see ***below***). First, the hospital provided a place for rest where staff could temporarily isolate themselves from their family. The hospital also guaranteed food and daily living supplies, and helped staff to video record their routines in the hospital to share with their families and alleviate family members' concerns. Second, in addition to disease knowledge and protective measures, pre-job training was arranged to address identification of and responses to psychological problems in patients with COVID-19, and hospital security staff were available to be sent to help deal with uncooperative patients. Third, the hospital developed detailed rules on the use and management of protective equipment to reduce worry. Fourth, leisure activities and training on how to relax were properly arranged to help staff reduce stress. Finally, psychological counsellors regularly visited the rest area to listen to difficulties or stories encountered by staff at work, and provide support accordingly.

A role for religion

The April 27/May 4, 2020 "Finding Hope" special issue of Time Magazine provided the following words of the Dalai Lama: "*This crisis shows that we must all take responsibility where we can. We must combine the courage doctors and nurses are showing with empirical science to begin to turn this situation around and protect our future from more such threats. … As a Buddhist, I believe in the principle of impermanence. Eventually, this virus will pass, as I have seen wars and other terrible threats pass in my lifetime, and we will have the opportunity to rebuild our global community as we have done many times before*". Modell (J Relig Health 2020, see ***below***) described three major ways that religious faith helped to sustain people's health and welfare in the midst of the broad social challenges posed by COVID-19 in Detroit, U.S.A., i.e. through church-based health programs (e.g. educational sessions), by providing hope, and providing social services (e.g. free grocery delivery to unemployed workers or student laptop loans).

Vulnerable groups

Elderly people

The outbreak of COVID-19 has raised great challenges for mental health services for older adults in the community in China. Yang (Lancet Psych 2020, see ***below***) noted that older adults have limited access to internet services and smart phones, and as such only a small fraction of older adults can benefit from such service provision. In addition, in most areas of China, clinically stable older adults with psychiatric disorders or their guardians usually need to visit psychiatric outpatient clinics monthly to obtain the maintenance medications. The mass quarantines and restrictions to public transport have inevitably become a major barrier to access maintenance treatments for this group.

Armitage (Lancet Public Health 2020, see ***below***) also predicted that self-isolation will disproportionately affect elderly individuals whose only social contact is out of the home, such as at day-care venues, community centres, and places of worship. Those who do not have close family or friends, and rely on the support of voluntary services or social care, could be placed at additional risk, along with those who are already lonely, isolated, or secluded. Dichter (Int Psychogeriatr 2020, see ***below***) noted that in spite of the restrictive infection control measures, the principles of person-centred care must be implemented in nursing home care. Infection management and person-centred care should be weighed carefully in order to maintain the residents' social participation, mental health and quality of life.

International migrant workers

Regardless of their communities' self-reliance and resilience, Liem (Lancet Psych 2020, see ***below***) noted that addressing the health needs of international migrant workers should be made an urgent public health priority. Compared with other international migrants, migrant workers encounter more barriers in accessing health services in host countries. Under normal conditions, they have a high burden of common mental disorders (e.g., depression) and

a lower quality of life than local populations. This situation could worsen during the COVID-19 epidemic due to the potential and fear of governmental-imposed quarantine and lost income. In the absence of reliable information in their own language, international migrant workers may not recognise the seriousness of the epidemic or receive accurate information on how to protect themselves from infection. However, most international migrant workers have smartphones, which can be a useful aid in providing informational and social support during the epidemic. For instance, WeChat (a Chinese social network platform) is used by international migrant workers in Hong Kong and Macau for sharing key health messages and official information to the community and providing one another with emotional support. It can, however, also spread inaccurate information and panic that could lead to IMWs delaying visits to health centres due to stigmatisation of those who are infected.

Homeless people

Tsai (Lancet Resp Med 2020, see ***below***) described various issues, which are unique to people experiencing homelessness, with regards to the COVID-19 epidemic. For instance, when cities impose a lockdown to prevent COVID-19 transmission, it is unclear whether shelter is provided for the large number of people experiencing homelessness, especially when considering that closures of shelters and other high-density communal settings (eg, drop-in centres and soup kitchens) are possible.

Implications of the COVID-19 pandemic

The impacts of the COVID-19 pandemic across the globe have been dramatic. COVID-19 is both a global health crisis and an international economic threat. Numerous publications have described how people's life have been affected. A few examples are provided below.

Impacts on healthcare systems

As a consequence of the pandemic, healthcare systems face various "collateral" issues. The physical and mental exhaustion of the healthcare workforce has been described. In addition, containment (and progressive de-confinement) measures, compounded by the economic recession, have been reported to affect mental health (e.g., anxiety, depression) as well as physical health (e.g., weight gain, unbalanced nutrition). Another important area under study relates to the delays of healthcare procedures unrelated to COVID-19. Cancer centres, for instance, have indeed postponed monitoring consultations and operations considered to be non-urgent. Maringe (Lancet Oncol 2020, see ***below***) estimated the impact of diagnostic delays over a 12-month period from the commencement of physical distancing measures in the UK up to 1, 3, and 5 years after diagnosis. The authors concluded that substantial increases in the number of avoidable cancer deaths are to be expected as a result of diagnostic delays due to the COVID-19 pandemic in the UK. They underscored the need to manage the backlog within routine diagnostic services to mitigate the expected impact of the COVID-19 pandemic on patients with cancer.

Impacts on the rest of society

Kniffin (Am Psychol 2020, see ***below***) reviewed the implications of the pandemic for employees, teams, and work organizations. The authors focused on emergent changes in work practices (e.g., working from home, virtual teamwork), emergent changes for workers (social distancing and loneliness; health and well-being; unemployment and inequality), as well as the importance of moderating factors (demographic characteristics; individual differences; organizational norms). They found obvious that COVID-19 will be recognized for changing the ways people work in fundamental ways.

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