Review: Micronutrient Selenium Deficiency Influences Evolution of Some Viral Infectious Diseases

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Abstract Recently emerged viral infectious diseases (VIDs) include HIV/AIDS, influenzas H5N1 and 2009 H1N1, SARS, and Ebola hemorrhagic fevers. Earlier research determined metabolic oxidative stress in hosts deficient in antioxidant selenium (Se) (<1 μMol Se/L of blood) induces both impaired human host immunocompetence and rapidly mutated benign variants of RNA viruses to virulence. These viral mutations are consistent, rather than stochastic, and long-lived. When Se-deficient virus-infected hosts were supplemented with dietary Se, viral mutation rates diminished and immunocompetence improved. Herein is described the role of micronutrient Se deficiency on the evolution of some contemporary RNA viruses and their subsequent VIDs. Distinguishing cellular and biomolecular evidence for several VIDs suggests that environmental conditions conducive to chronic dietary Se deprivation could be monitored for bioindicators of incipient viral virulence and subsequent pathogenesis.

Keywords Antioxidant · Ebola · HIV · Influenza · Reactive oxygen species (ROS) · SARS · Selenium bioavailability · Selenium deficiency · Viral infectious diseases (VIDs)

Introduction

Viral infectious diseases (VIDs), primarily influenzas and human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS), take personal, social, and economic tolls—HIV/AIDS ranks among the five global causes of death now and for the foreseeable future [1]. Influenza, in the United States alone, claims an estimated 36,000 people from annual epidemics and associated respiratory complications [2]; during pandemics, when the population has developed little immunity against novel influenza viruses, this figure can increase. Though socioeconomic/ecological factors contribute to the emergence and spread

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of various infectious diseases [1–3], a host's nutritional status was found to influence the etiology of specifically VIDs. This review describes the role of chronic micronutrient selenium (Se) deficiency on the evolution of some contemporary RNA viruses and their subsequent VIDs [4].

Significance of host Se status is based on the antioxidant properties of amino acid (aa) selenocysteine, the catalytic center of selenoenzymes. The glutathione peroxidase (GPx) family regulates biologic oxidative homeostasis by neutralizing metabolically produced "reactive oxygen species" (ROS: $H_2O_2^-$, O_2^-, OH·). Left unchecked, hyperoxidation disrupts biomolecules, cellular lipid membranes, organ tissues, metabolic pathways, and genetic mechanisms. Location and function of each tissue type of GPx is specific and not transferable [5]; intracellular glutathione peroxidase-1 (GPx1) resides in most body cells including red blood cells and, as measured in the blood, is a bioindicator of subject Se status.In the Se-adequate host, GPx1 is quiescent and non-essential [5] until chemically attracted to infection-induced ROS [6], for example, inhaled influenza A virus prompts pulmonary cellular production of ROS to attack the virus and to signal initiation of host cellular/biomolecular immune responses to destroy and clear the virus from the body:

> Influenza virus-laden sneeze → Healthy, Se-adequate host inhales influenza virus → Virus infects lung epithelium → Induces ROS (inflammation) → Chemoattracts GPx1 → Stimulates host proinflammatory chemokines → Induces dendritic cell activity, including polypeptide C1q [7] → Primes viral antigen-specific T cells → ↑ anti-inflammatory interferon-gamma (IFN-γ) and antibody immunoglobulin G (IgG) neutralization of viral antigen → inhibits virus replication and clears virus from host.

Persistence of parasitic viruses requires infecting host cells, pirating host resources, outmaneuvering host immune components and replicating. The generic RNA virus, equipped with a limited genome (3,000–30,000 nucleotides (nt)), codes for antigenic envelope glycoproteins, interior structural and non-structural proteins, and polymerases used for virion replication. Random point mutations, averaging $1–8 \times 10^{-3}$ nt substitutions per site per year [8, 9], and gene segment re-assortments alter viral modes of operation and, if successful for the virus, effectively outpace human immune system adaptations against the viruses. In the case of influenza A virus, 16 viable hemagglutinin (HA) and seven neuraminidase (NA) glycoproteins have contributed to novel, pandemic influenza A virus types H1N1, H2N2, H3N2, H5N1 [10]. As viral antigenic composition veers from host antibody recognition, the immune system is pressed to combat the particular viral invasion. Thus, commercial vaccines are routinely developed to anticipate and neutralize the various viral antigenic presentations, before pathogenesis.

During Se-deficient host conditions, transcription of GPx1 falls disproportionately to 10% Se-replete levels [11], and the limited nutrient is shunted elsewhere to meet other physiologic functions in Se-requiring tissues [12]. Discrepancy between concurrent heightened immune system requirements for GPx1 during viral infection and its diminished production help define the role of Se in the etiology of VIDs [13]. Initially, host vulnerability to ROS expresses increased bronchial epithelial cell mucus production [14] and lung pathology [15]; T cell proliferation is suppressed and immunocompetence impaired, including poor antibody response [13]. In addition, oxidative stress induces rapid mutation rates in some RNA virus types—often to virulence; under laboratory conditions, these mutations are not stochastic but consistent and quantifiable, and they are immediate, specific, and orders of magnitude faster than for the RNA virus genome under healthy host conditions [16]. Traceability and longevity of these mutations indicates optimal

biomolecular reconfiguration for stability and is a basis for viral virulence and pathogenesis.

While researching Keshan disease (KD), a myocarditis endemic to China [17], Beck et al.[18] discovered that women and children infected with Coxsackievirus B3 (CVB3) exhibited this lesioned heart condition when deficient in Se. KD occurs in geologic locales poor in soil Se available to dietary crops, including grains [19], on which inhabitants in rural, isolated regions subsist. Further epidemiology found that benign forms of both CVB3 and influenza virus type A rapidly mutate to virulence in hosts with Se-deficient status [20, 21]. Broome et al. [22] determined that a threshold of 1 μMol Se/L of host blood deterred rapid mutation of a live, attenuated poliomyelitis virus used as vaccine. Though dietary Se supplementation increased host blood Se levels, decreased viral mutation rates for each of these viruses and improved host immune responses including viral clearance from the hosts, mutated virulent RNA virions remained pathogenic and infectious, even to individuals with Se-replete status [20–22].

Method

To scope whether the findings of Beck and of Broome [20–22] apply to other VIDs, a world map depicting regions of "low soil-Se" (<0.01 mg/kg) [23] was superimposed with geographic origins of diseases [24] (Fig. 1). Pandemic influenzas type A (H2N2 "Asian," H3N2 "Hong Kong," and H5N1 "Avian" influenzas) and severe acute respiratory syndrome (SARS) originated in biogeochemically "Se-poor" regions of China; HIV/AIDS and Ebola hemorrhagic fevers (*Ebola "Zaire"*, *Ebola "Uganda"*) originated in nutrient-depleted
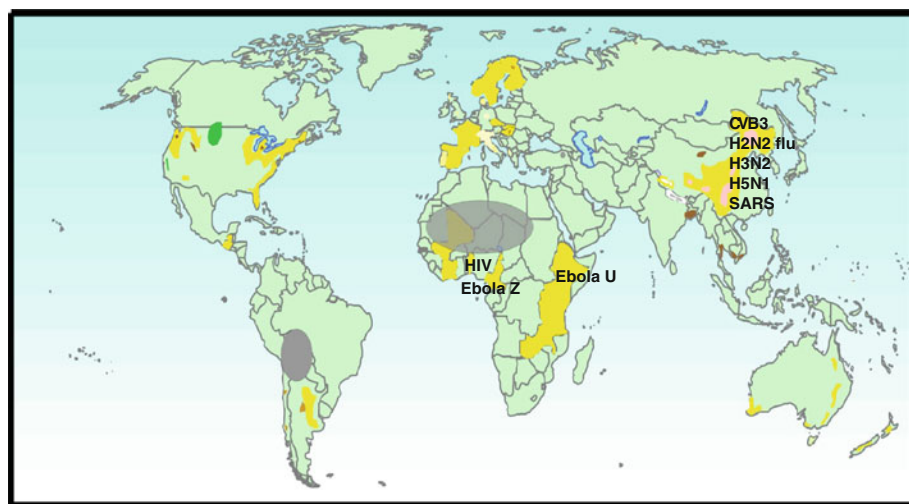

Fig. 1 Etiological origins of viral infectious diseases correlate with geologic regions of poor Se bioavailability from soils (<0.01 mg/kg, *yellow*) [23] to food crops. Some countries (U.S.A. and Scandinavia) fertilize with selenium for plant uptake. (*Pink patches* (China) indicate incidence of Keshan disease; *gray ovals* depict nutrient iodine deficiency, which seems not to influence the etiology of viral infectious diseases; and *brown patches* indicate high arsenic concentrations)

regions of sub-Saharan Africa (SSA). A literature review of worldwide human blood Se assays indicates sparse data from Se-poor regions of China and SSA, which can fall substantially <1 μMol Se/L (Fig. 2); reported diets there provide as low as 10–17 mcg of Se per day [25, 26], compared to the US recommended daily intake of 55 mcg of Se per day.

To substantiate the above observations, the literature was searched for geographic, ecologic, dietary, cellular, and biomolecular characteristics associated with RNA viruses and VIDs. This review does not consider the protective effects of antioxidant nutrients other than Se, nor any confounding Se antagonists, including toxic concentrations of nutrient iron, methyl-mercury, or other heavy metals, on the etiology of VIDs. Further, this review does not consider the effects of host Se-deficient status on the infectious oncological behavior of tumorigenic viruses such as the human variant of mouse mammary tumor virus or hepatitis virus on hepatoma.
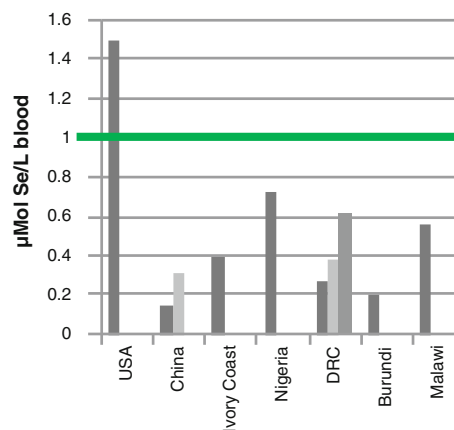
Results

Influenza A Virus

The eight-gene influenza genome encodes 12 known endogenous proteins, including HA/NA surface glycoproteins, three ribonucleic acid (vRNA) polymerase subunits (vRNP: PA, PB1, PB2), non-structural protein (NS1), and matrix proteins M1 and M2. During benign influenza A virus status, the abundant highly conserved matrix M1 protein (M1) transports recently replicated vRNP components from the host cell nucleus to membrane [27, 28]; nonetheless, transport of the viral M1–vRNP assemblage is hindered by host polypeptide C1q [29], housed in infection-responder dendritic cells (DCs). Under healthy host conditions, multifunctional C1q also induces antigen-specific T cell regulation of antibody IgG and cytokine IFN-γ impedance of viral replication [7].

When, however, Nelson et al. [21] infected both Se-adequate and Se-deficient mice with a mild influenza H3N2 virus strain, the influenza A virus matrix *M1* gene (*M1*), not the expected *HA* or *NA glycoprotein* genes, mutated rapidly, resulting in a virulent H3N2 variant in the Se-deficient mice; that is, 29 nucleotide (nt) substitutions, within interior nt numbers 309–740 of the *M1* segment, code for seven specific aa changes in the newly

Fig. 2 Human blood Se values <1 μMol Se/L [25, 26, 72–78] provide insufficient antioxidant protection for host immunocompetence against mutating RNA viruses
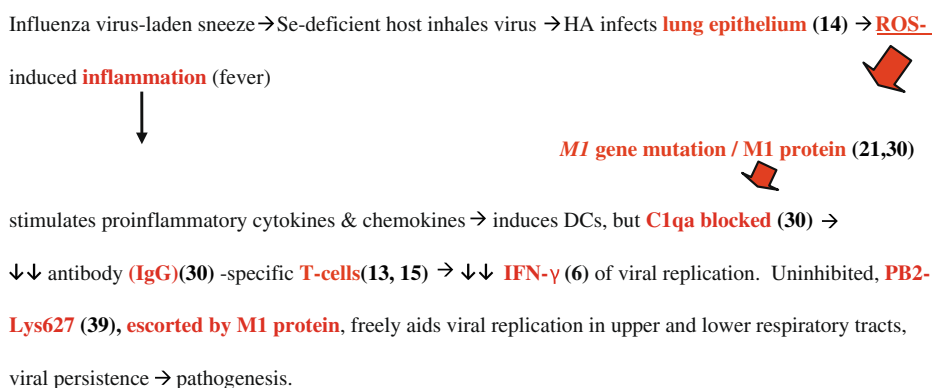
mutated M1. In this research, Se-deficient-induced ROS is the sole variable resulting in the M1 nucleotide/aa changes. Interior location of the several aa substitutions would alter biomolecular conformation of the M1 structure profoundly, and separate research describes a very different biomolecular mechanism than for the benign M1–C1q interaction [7, 29]. Zhang et al. [30] determined that the N-terminus of M1 firmly binds the globular domain of host C1q, thus blocking C1q stimulus of T cell activity, diminishing T cell use of antibody IgG and induction of INF-γ. As such, virulent M1 subverts DC-C1q functions [30] and the virus evades multiple host immune defenses.

In another mutated influenza A protein example, a single aa substitution (glutamic acid$^{(-)}$ (Glu), lysine$^{(+)}$ (Lys)) at position 627 of the vRNP PB2 subunit correlates with host Se status. Pathogenic avian influenza H5N1 virus [31], with virulent PB2-Lys627 [32], was recovered from dead waterfowl at Lake Qinghai, Qinghai Province, China [33]. While water quality Se assays for Lake Qinghai were not reported, the surrounding geologic landscape is nearly devoid of this essential micronutrient [34, 35]. H5N1-infected dead birds were also found in Hubei Province [36], known for localized regions of poor Se bioavailability [19, 37]; virulence was not detected, however, among asymptomatic H5N1-infected birds of poultry farms and markets of Hong Kong [38]. Asymptomatic bird species infected with influenza A strains 1918 and 2009 H1N1, H2N2, H3N2, and H5N1 carry PB2-Glu627 [27].

Kuzahara et al. [39] determined PB2-Lys^{+}627 lies within an "f-loop" of the PB2 subunit, which they calculate, strengthens PB2 affinity to other vRNP units to increase viral replication. Human pandemic influenza A strains 1918 H1N1, H2N2, H3H2, and H5N1 each contain virulent PB2-Lys627 [27].

Superimposing information of these ROS-induced changes, the immune system cascade becomes interrupted by Se-deficient **oxidative stressed** host conditions:

Influenza virus-laden sneeze→Se-deficient host inhales virus →HA infects **lung epithelium** (14) →**ROS-**

induced **inflammation** (fever)

M1 gene mutation / M1 protein (21,30)

stimulates proinflammatory cytokines & chemokines → induces DCs, but **C1qa blocked** (30) →

↓↓ antibody **(IgG)**(30) -specific **T-cells**(13, 15) → ↓↓ **IFN-γ** (6) of viral replication. Uninhibited, **PB2-Lys627** (39), escorted by M1 protein, freely aids viral replication in upper and lower respiratory tracts,

viral persistence → pathogenesis.

SARS Coronavirus

Virulence of SARS in humans begins with pulmonary cell entry of the novel coronavirus, SARS-CoV. The envelope "Spike" (S) glucoprotein of SARS-CoV exhibits two single aa residues, at positions 360 and 479, which both "determine" entry and neutralize host antibody receptor at the host cell surface [40, 41]. Palm civet (*Paguma larvata*) is the intermediary host for SARS-CoV [42], and civet-CoV retrieved from low-Se Hubei Province more closely relates to human SARS-CoV at determinant aa positions 360 and 479

than does the civet-CoV variant originating from "Se-adequate" Guangdong Province [40]. SARS/civet-like CoV originated in the Chinese horseshoe bat (*Rhinolophus macrotis*), and genomic sequencing found 71% of the bats assayed in Hubei Province carry the SARS-CoV precursor civet-like coronavirus [43]. That the most successful Spike glucoprotein mutation is retained pre-human infection may exemplify viral "adaptive evolution" stability [44].

HIV

The 1980 origin of pandemic HIV-1/AIDS was traced to specific chimpanzee populations infected with simian immunodeficiency virus (SIV_{cpz}) in southern Cameroon [45]. Contact or use of the infected primates as a food source may have facilitated transfer and evolution of the virus in humans [46].

Asymptomatic, SIV-infected primates carry several viral regulatory genes, including a poorly pathogenic SIV variant of the multifunctional *nef* gene. Benign *nef* gene, when transferred via SIV_{cpz} [47] to vulnerable humans, mutates, resulting in virulent nef proteins which interfere with host T cell functions and promote rampant virus replication [48]. Although the host vulnerability condition and genetic/biochemical mechanisms prompting conversion of benign SIV *nef* variant to HIV-1 virulence are yet to be identified, Hurwitz et al. [49] find that dietary supplementation of 200 mcg Se per day to HIV-infected subjects increased blood Se levels, increased T cell count and decreased viral load. Further, a 5-year randomized, double-blind placebo-controlled clinical trial in Tanzania found a 5% decrease in risk of mortality with each increase of 0.01 μMol Se/L blood from dietary supplementation in HIV-infected pregnant women [50].

EBOV

High mortality (~80%) Ebola hemorrhagic fever erupts episodically (1976–1979, 1994–1996, 2001–2005, 2007), spatially and temporally correlated with droughts [51] and subsequent diminished food production in the Congo Basin [3]. The challenge to find food during lean spells takes human and non-human primates to remote highland fruit bat habitat where several bat species host the Ebola virus (EBOV) [52, 53]. Though outwardly asymptomatic, EBOV-infected bat contact with primates, including humans, is highly virally infectious and contagious, and pathogenic die-off from Ebola hemorrhagic fever during these episodes is severe. The "wild type" (wt) Ebola virus protein 35 (VP35) functions to inhibit host production of interferon transcription factors (INF-3 and INF-7) and aid viral replication [54]; critical to wt VP35 protein virulence are both the interferon inhibitory domain "fold" [54], created by an aa arginine residue at VP35 position 312 [55], and the wt Ebola VP35 use of the host transcription mechanism for interferon production to block immunity against the virus [56].

While the effect of host Se status on Ebola virus virulence is not yet verified, asymptomatic EBOV-infected bats and human survivors of the disease produce virus-specific IgG antibodies [57, 58], whereas T cells and their induced immunoglobulins and INF-γ are undetected in symptomatic EBOV-infected mammals, including humans, which succumb to the systemic disease [59]. This pattern of disabled T cell function is reminiscent of Se-deficiency effects on influenza virus-infected T cells [6, 13–15]. The hunger experienced during the above-described climatic dry spells could be caloric, but if

prolonged, also an individual expression of undernutrition and malnutrition, including Se deficiency.

Conclusions

Regions of the globe are void of Se bioavailable from soils for food crop uptake [23] and adequate human nutrition. Worldwide, soils average 0.4 mg Se/kg of soil; "Se-poor" soils in China range between 0.004 and 0.48 mg Se/kg, but Se bioavailability to crops, regardless of soil concentrations, is controlled by biogeochemical factors including soil mineralogy, acidity, oxidation potential, and presence of organic matter [19, 37, 60]. Wide variability in Se accumulation in grains grown on adjacent heterogeneous source rocks in Hubei Province demonstrates this influence [19]:

Rice, 0.079, *0.017*, 0.063 mg Se/kg grain
Wheat, 0.087 *0.018*, 0.052 mg Se/kg grain
Corn, 0.050, *0.015*, 0.048 mg Se/kg grain

In Africa, the African Soils Information Service reports degraded, nutrient-depleted conditions for >500 million hectares of SSA soils, and that one third of the population there is "chronically hungry" [61]. For example, though relatively urbanized, and researched, 50% of children in South Africa consume less than half the caloric and nutrient requirements needed for sound health; 70% of a surveyed population "perceive their households to be food insecure and 30% of the households report that their children went to bed hungry, a percentage that increases as incomes decline" [62]. Undernutrition and Se deficiency, especially during pre-natal and childhood periods, have lasting adverse effects which influence physiologic development of immature immune systems and subsequent impaired immunocompetence in post-adolescent years [63, 64]. These dietary and antioxidant Se-deficient nutritional conditions contribute to the physiologic oxidative stress conducive to impaired immune systems and RNA viral mutations, which can be virulent and pathogenic. Table 1 synopsizes the known geographic, ecologic, edaphic, and epidemiologic factors contributing to the VIDs discussed.

The Future

Despite the emergence of the above-described diseases in China and SSA, and the 2007 outbreaks of both poliomyelitis in Nigeria (353 cases) [65] and Ebola "Uganda" [66], etiological origin of infectious RNA viral virulence is not restricted to these geographic regions. Epidemic optic and peripheral neuropathy in Cuba during the early 1990s was traced to infection by otherwise benign Coxsackievirus A9 during an extended period of food shortages, prompting virulence [67].

Etiology of these VIDs suggests that vulnerable populations in any geographic region enduring chronic nutritional Se deprivation, for any reasons, could become spawning grounds for virulence of innate benign but opportunistic RNA viruses. If infectious, the virulent virus can be transferred even to individuals with Se-adequate status. Monitoring incipient hot spots for immune system biomarkers, agricultural productivity, and adequate and nutritious food supply to local populations, is a small order for helping to tame local or global RNA viral virulence.

Table 1 RNA viruses, geographic origins, and vectors of several viral infectious diseases

Virus	VID common name	Location(s): soil Se factors, Se in blood (µMol/L)	Vector	References
RNA Picornaviridae Coxsackievirus B3	Keshan disease myocarditis	Keshan County, Heilongjiang Province, China; Hebei Province; Hubei Province: <7.6 pH, high soil OM, 10 mcg Se/day diet → 0.16–0.32 µMol Se/L blood	Not known (grain, soil, soil microbiota?)	[17–19, 25, 26, 37, 60]
RNA Orthomyxoviridae	1918 "Spanish" influenza	Partial Eurasian "origin"	Avian → Swine, <1918	[8, 27, 28, 68, 69]
Influenza A H1N1	2009 "Swine" influenza		Swine *NA* and matrix *M* genes of Eurasian origin; avian PB2-Glu 627, 1918 human PB2-Lys627; 2009 human PB2-Glu627	
Influenza A H2N2	1957 Asian influenza	Sanjiang NR, Heilongjiang Province, China	Mallard; human PB2-Lys627	[27, 32, 70]
Influenza A H3N2	1968 Hong Kong influenza	Heilongjiang Province, China	Human → swine; human PB2-Lys627	[27, 32, 69]
Influenza A H5N1	>1997 Avian influenza	Lake Qinghai, Qinghai Province, China—very low Se (grazing yak w 1/3 blood Se of domestic yak); found in Hubei Province, not in Hong Kong	Migratory waterfowl, lesioned; Eurasian *M gene*; avian PB2-Lys627 →humans	[27, 31–38]
RNA Coronaviridae SARS-CoV	SARS (2002–03)	Hubei Province, China; strong lithologic heterogeneity, including low-Se and low-Se bioavailability	Chinese horseshoe bat (*Rhinolophus acrotis*)→ Himalayan palm civet (*Paguma larvata*) →Humans "Spike" glucoprotein aa Δs at positions 360 and 479	[19, 37, 40, 42, 43, 60]
RNA Lentiviridae HIV retrovirus	HIV-1 (early 20th C, and again, early 1980s); HIV-2 (~1940) HIV/AIDS	Nutrient (Se)-depleted soils Cameroon; Gabon	SIV Chimpanzee (*Pan t. troglodytes*); *nef gene Δ*	[23, 45–47, 71]
		Guinea-Bissau; Côte d'Ivoire (Taï Forest)	SIV Sooty mangabey (*Cercocebus atys atys*)	
RNA Filoviridae Ebola virus	Ebola "Zaire" (1976–79, 1994–96, 2001–5)	Mayinga, DRC; Kikwit, DRC; Mendemba, Gabon	Fruit bats (ssp.) → gorillas, chimpanzees, humans; VP35 Arg at position 321 → humans	[3, 23, 51–55, 57–59, 66]
	Ebola "Uganda" (2001, 2007) Episodic, drought correlated	Bundibugyo, Uganda, volcanic Se-poor soils	Infected non-human primates → humans	

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