Int J Pept Res Ther (2016) 22:135–141
DOI 10.1007/s10989-015-9491-7

Ebola Outbreak in West Africa; Is Selenium Involved?

Nouran Abd-ElMoemen[1] · Ahmed Menshawy[2] · Ahmed Negida[3] · Marwa Alaa El-Din[4] · Ahmed Kamel[1] · Alaa Ehab Farouk[1]

Accepted: 22 August 2015 / Published online: 15 September 2015

Abstract One of the current international public health emergencies is the outbreak of Ebola virus disease (EVD), requiring extraordinary response. The current outbreak in West Africa is the most dangerous since Ebola was first discovered on 26 August 1976. Till January 6th 2015, It resulted in 13,387 laboratory confirmed human cases and 8274 deaths. Ebola virus has 5 strains, 4 are pathogenic in humans while the 5th strain Ebola reston strain is not. The current outbreak is caused by Ebola most pathogenic strain, Ebola Zaire strain whose genome differs from that of Reston Ebola virus strain, by the existence of several open reading frames containing large numbers of UGA codons. These codons act as stop codons and in addition they may encode for Selenocysteine, the 21st aminoacid, which is essential for the formation of Selenoproteins. Selenoproteins are integral to the metabolism and have been linked to the progression of certain viral diseases. In this review, we discuss the relation between Selenium and the progression of the current EVD in Africa supported by geographical distribution of Se and genetic evidence.

✉ Nouran Abd-ElMoemen
nouran.abdelmoemen@gmail.com;
nuran.a.fathi@students.kasralainy.edu.eg

[1] Kasr AlAiny Medical School, Cairo, Egypt

[2] Faculty of Medicine, Al-Azhar University, Cairo, Egypt

[3] Faculty of Medicine, Zagazig University, Zagazig, Egypt

[4] Department of Biotechnology, Faculty of Science, Cairo University, Giza, Egypt

Keywords Selenium · Selenoproteins · Selenocysteine · Ebola · EVD · Zaire · EBOV · Outbreak · SeC · Immunity

Introduction

One of the most threatening events nowadays is the Ebola outbreak (Biomedical and environmental sciences 2014). Ebola is a viral disease caused by the Ebola virus which is an enveloped, non-segmented, negative-stranded RNA virus. Ebola is of the family "Filoviridae" which includes three species: Cuevavirus, Marburgvirus, and Ebolavirus, and it is divided into 5 subtypes: Sudan, Taï Forest, Reston, Bundibugyo, Zaire. The current outbreak in West Africa is caused by the Zaire species (EBOV) and it is the most dangerous outbreak since Ebola was first discovered (Emergence of Zaire Ebola virus disease in Guinea—NEJM 2015a). It is thought that the Ebola virus is mainly transmitted through the fruit bats of the Pteropodidae family (WHO/Ebola virus disease 2014). The virus is transmitted through close contact with blood, body fluids, secretions or organs of infected animals. Then, it can be transmitted by human-to-human contact with the blood, body fluids, secretions or organs of infected person and with contaminated surfaces ad materials. The incubation period, the period from infection to the onset of the symptoms, of the Ebola virus disease (EVD) ranges between 2 and 21 days. The first symptoms are fever fatigue, headache, sore throat, and muscle pain followed by diarrhea, vomiting, rash, and symptoms of impaired liver and kidney. Also, EVD may be accompanied by internal and external bleeding in some cases. Treatment, by rehydration through oral and intravenous fluids and treatment of symptoms, improves survival. There are 2 vaccines under trial but no licensed vaccines are proven yet (Biomedical

and environmental sciences 2014; WHO/Ebolavirus disease 2014).

Epidemiology

A long nine months till last august, 2014, more than two thousands were diagnosed with Ebola in just four African countries (Ki 2014). First Ebola case was in 1976 in a 44-year old man in Congo. He died 6 days later by a severe hemorrhage and his doctor accidentally infected himself with the virus (Emond et al. 1977). In the same year first large outbreak occurred in Sudan. Total 284 cases diagnosed by Ebola, 213 were in Maridi. 67 case in Nazara and fewer numbers in Tembura and Juba (1978a). Another break was in Congo few months after Sudan. 318 cases were reported by Ebola symptoms. Most cases was concentrated around Yambuku. Out of 318 cases 280 died when 38 survived (1978b). A single case was diagnosed again in June 1977 in a 9 years old girl in Zaire, Congo (Heymann et al. 1980). Uganda had the third Ebola virus outbreak. Out of 425 cases, 224 were died by hemorrhagic fever (Lamunu et al. 2004). Some studies showed an association between eating and hunting fruit bats and Ebola virus outbreak as in Kikwit 1995, Mweka 2007, Gulu 2000 and Yambio (Sudan) 2004 (Muyembe-Tamfum et al. 2012). The current outbreak has killed more than 1000 case till now. Linear rapid increase in that number is very likely (Ebola 2014). After those 40 years of studying that disease, it still a fetal uncontrolled disease that attack without previous warning (Zhang and Wang 2014). A recent review article showed that along those 40 years, 23 outbreaks in Africa were recognized. Those outbreaks were condensed in South Sudan, Congo, Côte d'Ivoire, Gabon, Uganda and Guinea (Pigott et al. 2014).

EBOV Fatality Rates (Previous Till 2014)

Zaire EBOV (EBOV) was first detected in 1976 (Jacob and Piot 1976). The total fatality rate for EBOV from 1976 to 2008 was 79 %. Fatality rates in previous outbreaks are illustrated in Table 1 [adopted from Derek Gartherer (Gatherer 2014)] However, when confirming the present Guinea outbreak by full genome sequencing, the current strain was found to be an outlier from Zaire ebolavirus (Emergence of Zaire Ebola virus disease in Guinea—NEJM 2015b). The first report about EBV outbreak 2014 was in 22 March 2014 from Guinea; it reported 49 cases resulted in 29 deaths with a 59 % fatality rate. Till 20 April 2014, there were 242 suspected cases in Guinea and Liberia resulted in 147 deaths with a 61 % fatality rate. Cases in Liberia was doubling every 15–20 days; and in Sierra Leone, cases were doubling every 30–40 days. By June 18, there were a combined total of 528 cases (including laboratory-confirmed, probable, and suspected cases) and 337 deaths with a fatality rate = 64 % reported in the three countries (Guinea, Liberia, Sierra Leone). This outbreak was the largest EVD outbreak ever documented, since the largest one before 2014 was that of Uganda during 2000–2001, there were a total of 425 cases resulted in 224 deaths with a fatality rate = 53 % (Emergence of Zaire Ebola virus disease in Guinea—NEJM 2015b). By 31 August 2014 there were a total 3,685 cases (probable, confirmed and suspected) cases and 1841 deaths with a 50 % fatality rate; Table 2 illustrates the Widespread and intense transmission as at 31 August 2014 from WHO report (WHO/Ebola virus disease 2014). Center of disease control (CDC) developed Ebola Response modeling tool to estimate the number of future cases; and based on these estimation a total 8000 cases within west Africa are expected by 30 September 2014 (Gatherer 2014).

Selenium and the Immune System

Selenium is hypnotized to affect body immunity as a decrease in serum selenium level by about 50 % in elder women more than 90 year was associated by significant decrease in Natural Killer cells activity ($P = 0.018$) (Ravaglia et al. 2000). Selenium is believed to decrease risk of many disease associated with increased level of free radicals or decrease of antioxidants including viral

Table 1 Illustrates the previous outbreaks of Zaire EBOV before 2014 [Adopted from Derek Garther (Gatherer 2014)]

Year (s)	Country	Cases (s)	Death (s)	Case fatality (%)
2007–2008	DRC	296	201	68
2005	Congo	12	10	83
2003	Congo	178	157	88
2001–2002	Congo + Gabon	125	98	78
1996	Gabon	91	66	73
1995	DRC	315	254	81
1994	Gabon	52	31	60
1976–1977	DRC	319	281	88

Table 2 Illustrates widespread and intense transmission as at 31 August from WHO report

Country	Case definition	Total	Total (deaths)	Case fatality rate (%)
Guinea	Confirmed	579	343	59
	Probable	150	149	99
	Suspected	42	2	5
	All	771	494	64
Liberia	Confirmed	403	271	67
	Probable	815	373	46
	Suspected	480	227	47
	All	1698	871	51
Sierra Leone	Confirmed	1107	430	39
	Probable	37	34	92
	Suspected	72	12	17
	All	1216	476	39
All	All	3685	1841	50

expression (HIV, AIDS) as it enter in the structure of four glutathione peroxidases (selenoperoxidases) so help as cell antioxidant system against. So it is important to have adequate selenium amounts in food (Arthur 2000; Klein 2004; Zachara et al. 2006).

Several papers discussed the role of Selenium in maintaining the immune system and its function. Selenium has been suggested to be crucial for an optimal immune response. It was found to affect the acquired and innate immune systems (Henley 1976). Selenium-deficient humans were found to have decreased IgM and IgG titres, this decrease was improved when Selenium supplementation was introduced (Kiremidjian-Schumacher and Roy 1998). During Selenium deficiency, Lymphocytes exhibit less proliferative powers. Also synthesis of leukotriene B4, an important factor for neutrophil chemotaxis, is impaired (Hatfield et al. 2006). It is worth mentioning that recovery from Ebola virus infection was encountered in patients who managed to develop efficient Ig(G)s against the Ebola virus (Becquart et al. 2014). Selenium plays an important role in hemostasis through affecting the Prostacyclin (PG12)/Thromboxane (TXA2) ratio (Meydani 1992; Universitdl 1994; Ramanathan and Taylor 1997). PGI2 and TXA2 are eicosanoids that are formed from arachidonic acid. TXA2 is released from platelets and it promotes vasoconstriction and platelet aggregation, while PGI2 is released from the vascular smooth muscle cells and the endothelial cells and it acts as a platelet aggregation endogenous inhibitor and it also is a potent vasodilator (Hamberg et al. 1975; Smith 1980). In a human study, Selenium supplementation decreased the levels of TXA2 but did not affect the levels of PGI2 (Perona et al. 1990). Hemostasis is dependent on the balance between PG12 and TXA2, and so the increase in the PGI2/TXA2 ratio, which is caused by administering Selenium supplementation, has been suggested as a possible therapeutic agent to decrease clotting, especially that of disseminated intravascular coagulopathy (DIC) that accompanies Ebola hemorrhagic fever is naturally expected to result in disrupted hemostasis (Ramanathan and Taylor 1997). Selenium enters in the formation of the 21st amino acid, Selenocysteine (SeCys) which is incorporated into the active site of glutathione peroxidase (GPx) (Beck et al. 2004; Ramoutar and Brumaghim 2010). GPx are a family of enzymes that combat oxidative stress, they neutralize the metabolism byproduct reactive oxygen species ROS. ROS is known to damage tissues and cell membranes, and they disrupt the body's metabolism and genetics (Harthill 2011). Intracellular cytosolic GPx performs its function by reducing intracellular hydrogen peroxide (H_2O_2) into water, thus protecting against ROS formation (Ramoutar and Brumaghim 2010). The close relation between Se and GPX is demonstrated in the fact that optimal GPx activity has been used as a measurement for selenium intake requirements (Thomson 2004).

Adverse Effects

Serum or urine plasma levels reflect the recent intake of selenium when analysis of hair or nail content of selenium reflect the long term intake (Erdman et al. 2012). Normal serum selenium level differs according to age. In 6–11 years old person it is 89.0–142 µg/dL and 104.0–187.0 µg/dL in >12 years old persons in both sexes (Caldwell 2011–2012).

On April 15, 2013, the food and drug administration (FDA) organization announced a rule to add selenium to the infant formulas and established its minimum (2.0 µg/100 kcal) and maximum levels (7.0 µg/100 kcal). They ranked it as the 30th mandatory nutrient for infants (Nutrition).

The average required daily intake dose for nearly all healthy individuals (97–98 %) equals 55 µg for both sexes.

Recommended amount for pregnant women is 60 and 70 μg for lactating women daily (Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids 2014). The tolerable upper intake level (TUIL) equals 400 μg daily (Bjelakovic et al. 2012). Selenium become toxic at concentrations >1 to 5 mg/kg daily (Nathues et al. 2010).

Route of administration of selenium may be associated with some different adverse effects. Acute inhalation commonly associated with irritation of respiratory mucous membranes, bronchial spasm, dyspnea and chemical pneumonia. Oral route commonly associated with decrease of white blood cells count and increase in lymphocytes, nausea, vomiting, diarrhea and abdominal pain when pulmonary edema and tachycardia are less commonly recorded (The 2000).

It is believed that the a syndrome characterized by impaired vision, aimless wandering behavior, reduced consumption of food and water, and finally paralysis and death occur in animals after consumption of plants high in selenium. Acute selenium poisoning is potentially lethal due to cardiocirculatory failure and pulmonary edema (Olson 1986; Nogueira and Rocha 2011). It also was found that the average survival time for dogs had selenite at 1.5 mg Se/kg body weight was significantly shorter for those anesthetized and breathing oxygen than for those, anesthetized or un anesthetized, breathing room air (Olson 1986).

A study on 72 Columbia x Suffolk sheep divided into three groups, control, low selenium and high selenium level. The HiSe group was exposed for 4 weeks to elevated Se forage more than 49.0 ppm Se dw and drinking water 340–415 ppb Se. Estimated daily exposure to Se was 0.26 mg Se/kg/d only one sheep out of 24 of the group died due to Se toxicity. Se in liver, kidney, and skeletal muscle was 3.90, 1.90 and 0.70 ppm respectively(Fessler et al. 2003).

High selenium levels above TUIL have many adverse effects including increasing the risk of type 2 diabetes mellitus as high level of GPx can interfere with insulin signaling (Rayman and Stranges 2013). It also found to increase risk of amyotrophic lateral sclerosis (Nogueira and Rocha 2011). No evidence that selenium is carcinogenic in human in contrast to animals (Rowland 2006).

Selenium Status of West African Population

Selenium is present in different kinds of meat, kidney, liver, seafood, and crops. The literature is lacking sufficient information regarding the distribution of Selenium in African soils, which is regarded as a determinant, along with the biogeochemical characteristics of the soil, of Selenium availability in the grown grains and seeds (Davies 2013). Trials have been made to estimate the Selenium status of the African population(Chilimba et al. 2011; Hurst et al. 2013; Joy et al. 2014). We found two papers that ventured to make Selenium supply and deficiency maps for the entire continent of Africa (Hurst et al. 2013; Joy et al. 2014). For west Africa, both papers Calculated the Selenium supply per capita as a product of the food supply data, as provided by the FAO, and the food composition data, as provided by Stadlmayr et al. (2010). The problem with this approach is that the food composition data in the Stadlmayr et al. (2010) paper were measured according to the Selenium values in foods grown in foreign countries, and so cannot be used as an estimate of the Selenium content in West African foods (Table de Composition Des Aliments ́dAfrique de ÍOuest West African Food Composition Table). Selenium has been linked with the progression of several diseases, including: viral infections, such as Human immunodeficiency virus (HIV) and Coxsackie virus, cancer, cardiovascular diseases, thyroid dysfunction, male infertility, pregnancy miscarriage, depression, and inflammatory conditions (Bunnell 2007; Rayman 2000; Tapiero et al. 2003; Johnson et al. 2010; Davies and Mundalamo 2010; Fairweather-Tait et al. 2011; Kishosha et al. 2011). A paper used that correlation between Selenium and some of those diseases to estimate the Selenium distribution throughout Africa. The incidence of HIV was used to make a map of Selenium-deficient regions in Africa (Oldfield 1999). This method though, does not discuss other confounding variables that affect disease incidence and so, we think, researchers should not rely on that method solely.

The Genetics of Selenocysteine

UGA codon translation Selenocysteine is represented by the nucleotide sequence UGA, which is normally a stop codon, but in the presence of the "right circumstances" it can code for Selenocysteine (Taylor and Nadimpalli 1997; Ramanathan and Taylor 1997; Donovan and Copeland 2010). Selenocysteine insertion sequence (SECIS) is a stem-loop structure in the genome of prokaryotes and eukaryotes that deliberately encode selenoproteins (Bertram et al. 2001). Several factors control the efficiency of terminating the translation at UGA codons and thus failure of their expression as Selenocysteine. One of these factors is whether there is a purine or a pyrimidine base following the UGA codon. It has been suggested that the presence of purine favors termination while the presence of pyrimidine favors translation of Selenocysteine (Tate et al. 1995). Although this tendency is not regarded as absolute and the presence of purine can be overcome if there's a need for Slenocysteine (Ramoutar and Brumaghim 2010).

Factors Controlling Frameshifts

Frameshifting is a process that occurs when ribosomes shift their position on the mRNA by a nucleotide (or several nucleotides) and in doing so, altering the downstream sequence of codons during the translation of a protein strand. Frameshifts are common in viruses, especially −1 frameshifts where the ribosome moves by the distance of 1 nucleotide in the 5‘ direction (Weiss 1991; Brierley 1995). −1 frameshift is usually of the “tandem slippery codon” type (Weiss 1991). The presence of two cis-acting structures predispose for the frameshift, those structures are: a slippery codon and a secondary structure (Theis et al. 2008). A slippery codon is a sequence that facilitates for the shift to occur, a great example is a heptameric shift sequence “X XXY YYZ” (the preshifted sequence), but other deviations are also possible (Theis et al. 2008; Ramoutar and Brumaghim 2010). The secondary structure can be a pseudoknot or a stem-loop (Theis et al. 2008). Pseudoknots are ideal frameshifters as they help with ribosomal pausing, which promotes frameshifting but is not necessary for it (Theis et al. 2008). In HIV, a disease that is known for its relation with Selenocysteine (Harthill 2011), there’s a slippage sequence at which the ribosome translocates by only one nucleotide while two tRNA are bound, this results in a −1 frameshif (Ramanathan and Taylor 1997). Frameshifts make it possible for a genetic sequence to be translated without being preceded by a start codon (Ramoutar and Brumaghim 2010).

Computational Analysis of the Ebola Virus Genome

The Ebola virus is a filamentous unsegmented negative sense RNA virus of the family Filoviridae. Its genome encodes two nonstructural proteins (secreted glycoprotein and small soluble glycoprotein) and seven structural proteins (glycoprotein, nucleoprotein, L, and virion proteins: VP-40, VP-35, VP-30, and VP-24) (Choi and Croyle 2013). The strain that is responsible for the 2014 epidemic is the Ebola Zaire strain (EBOV) (Emergence of Zaire Ebola virus disease in Guinea—NEJM 2015b). The Ebola virus (EBOV) genome has been the target of interest of some computational genetic studies which suggested the possibility of its selenocysteine translation. In the Ebola Zaire genome, there are two open reading frames (ORFs), or rather called potential protein coding regions (PPCRs), present in the −1 frame and they overlap the major nucleoprotein gene. The first one contains 17 UGA codons, has a heptameric frameshift sequence “UUUCCCU” near the start of the PPCR, and an RNA pseudoknot 8 nucleotides downstream. Successful shifting, at that site, should result in a nucleoprotein residue fused to a strand containing 16 Selenocysteine residues. Another frameshifting sequence is present and is followed by a potential pseudoknot. Shifting at that site should result in a protein containing 11 Selenocysteine residues. In addition, the last 14 UGA codons, from the 5′-end, are each followed by a pyrimidine base which is thought to favor read-through. The second PPCR contains 11 UGA codons and, although it’s not preceded by a start codon, it has the potential of being expressed through RNA splicing or editing (Ramoutar and Brumaghim 2010). All Ebola subtypes were found to express their structural glycoproteins over two reading frames that are expressed through RNA editing(Sanchez et al. 1996). Other PPCRs were found overlapping the coding regions for the other Ebola proteins (such as VP40, VP35, VP30, and VP24). They also carry potential SECIS elements in their mRNA. All of this hints that Selenocysteine could be nonspecifically translated as a termination to non-functioning frame-shifted strands of protein or it could be translated as part of functional proteins (Ramoutar and Brumaghim 2010).

Conclusion

(1) Selenium blood level seems to have a serious effect on the clinical picture of patients with Ebola virus disease.
(2) There aren’t enough information on the Selenium intake in Africa, which is strongly affected by the Selenium levels in the soil, and that latter information is not routinely measured when assessing the micronutrient content of soil.
(3) The authors of this paper find it extremely important to test the blood samples from Ebola patients for their Selenium levels and their relation with the disease outcome should be carefully studied.
(4) If Selenium supplements are decided to be given by the physician, symptoms of toxicity should be carefully anticipated as Selenium has a narrow therapeutic index.

Acknowledgment This paper was not funded by anyone or any institution.

Compliance with Ethical Standards

Conflict of interest The authors of this paper declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

Arthur JR (2000) The glutathione peroxidases. Cell Mol Life Sci 57:1825–1835

Beck MA, Handy J, Levander OA (2004) Host nutritional status: the neglected virulence factor. Trends Microbiol 12:417–423. doi:10.1016/j.tim.2004.07.007

Becquart P, Mahlakõiv T, Nkoghe D, Leroy EM (2014) Identification of continuous human B-cell epitopes in the VP35, VP40, nucleoprotein and glycoprotein of Ebola virus. PLoS One 9:e96360. doi:10.1371/journal.pone.0096360

Bertram G, Innes S, Minella O et al (2001) Endless possibilities: translation termination and stop codon recognition. Microbiology 147:255–269

Biomedical and environmental sciences (2014). http://www.besjournal.com/Articles/Archive/2014/No8/201409/t20140904_104151.html. Accessed 31 Dec 2014

Bjelakovic G, Nikolova D, Gluud LL et al (2012) Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst Rev 3:CD007176

Brierley I (1995) Review article ribosomal frameshifting on viral RNAs. J Gen Virol 76:1885–1892

Bunnell JE, Finkelman RB, Centeno JA, Selinus O (2007) Medical Geology: a globally emerging discipline. Geol Acta 5(3):273–281

Caldwell KL (2011–2012) Zinc, copper and selenium serum serum multi-element ICP-DRC-MS. http://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/CUSEZN_G_met_serum_elements.pdf

Chilimba ADC, Young SD, Black CR et al (2011) Maize grain and soil surveys reveal suboptimal dietary selenium intake is widespread in Malawi. Sci Rep 1:72. doi:10.1038/srep00072

Choi JH, Croyle MA (2013) Emerging targets and novel approaches to Ebola virus prophylaxis and treatment. BioDrugs 27:565–583. doi:10.1007/s40259-013-0046-1

Davies TC (2013) Geochemical variables as plausible aetiological cofactors in the incidence of some common environmental diseases in Africa. J Afr Earth Sci 79:24–49. doi:10.1016/j.jafrearsci.2012.11.002

Davies TC, Mundalamo HR (2010) Environmental health impacts of dispersed mineralisation in South Africa. J Afr Earth Sci 58:652–666. doi:10.1016/j.jafrearsci.2010.08.009

Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids (2014). http://www.nap.edu/openbook.php?record_id=9810. Accessed 30 Nov 2014

Donovan J, Copeland PR (2010) The efficiency of selenocysteine incorporation is regulated by translation initiation factors. J Mol Biol 400:659–664. doi:10.1016/j.jmb.2010.05.026

Ebola (2014) New challenges, new global response and responsibility—NEJM. http://www.nejm.org/doi/full/10.1056/NEJMp1409903. Accessed 31 Dec 2014

Emergence of Zaire Ebola virus disease in Guinea—NEJM (2015a). http://www.nejm.org/doi/full/10.1056/NEJMoa1404505#t=article. Accessed 16 Jan 2015

Emergence of Zaire Ebola virus disease in Guinea—NEJM (2015b). http://www.nejm.org/doi/full/10.1056/NEJMoa1404505#t=articleTop. Accessed 1 Jan 2015

Emond RT, Evans B, Bowen ET, Lloyd G (1977) A case of Ebola virus infection. Br Med J 2:541–544

Erdman JW, Macdonald IA, Zeisel SH (eds) (2012) Present knowledge in nutrition. Wiley-Blackwell, Oxford

Fairweather-Tait SJ, Bao Y, Broadley MR et al (2011) Selenium in human health and disease. Antioxid Redox Signal 14:1337–1383. doi:10.1089/ars.2010.3275

Fessler AJ, Moller G, Talcott PA, Exon JH (2003) Selenium toxicity in sheep grazing reclaimed phosphate mining sites. Vet Hum Toxicol 45:294–298

Gatherer D (2014) The 2014 Ebola virus disease outbreak in West Africa. J Gen Virol 95(pt 8):1619–1624. doi:10.1099/vir.0.067199-0

Henley WL (1976) The immune response. Pediatr Ann 5:369–371

Hamberg M, Svensson J, Samuelsson B (1975) Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides. Proc Natl Acad Sci 72:2994–2998. doi:10.1073/pnas.72.8.2994

Harthill M (2011) Review: micronutrient selenium deficiency influences evolution of some viral infectious diseases. Biol Trace Elem Res 143:1325–1336

Hatfield DL, Berry MJ, Gladyshev VN (eds) (2012) Selenium: Its molecular biology and role in human health. Springer-Verlag, New York. doi:10.1007/978-1-4614-1025-6

Heymann DL, Weisfeld JS, Webb PA et al (1980) Ebola hemorrhagic fever: Tandala, Zaire 1977–1978. J Infect Dis 142:372–376. doi:10.1093/infdis/142.3.372

Hurst R, Siyame EWP, Young SD et al (2013) Soil-type influences human selenium status and underlies widespread selenium deficiency risks in Malawi. Sci Rep 3:1425. doi:10.1038/srep01425

Jacob W, Piot P (1976) In the. 573–574

Johnson CC, Fordyce FM, Rayman MP (2010) Symposium on "Geographical and geological influences on nutrition": factors controlling the distribution of selenium in the environment and their impact on health and nutrition. Proc Nutr Soc 69:119–132. doi:10.1017/S0029665109991807

Joy EJM, Ander EL, Young SD et al (2014) Dietary mineral supplies in Africa. Physiol Plant 151:208–229

Ki M (2014) What do we really fear? The epidemiological characteristics of Ebola and our preparedness. Epidemiol Health 36:e2014014. doi:10.4178/epih/e2014014

Kiremidjian-Schumacher L, Roy M (1998) Selenium and immune function. Z Ernahrungswiss 37(Suppl 1):50–56

Kishosha PA, Galukande M, Gakwaya AM (2011) Selenium deficiency a factor in endemic goiter persistence in sub-Saharan Africa. World J Surg 35:1540–1545. doi:10.1007/s00268-011-1096-5

Klein EA (2004) Selenium and vitamin E cancer prevention trial. Ann N Y Acad Sci 1031:234–241. doi:10.1196/annals.1331.023

Lamunu M, Lutwama JJ, Kamugisha J et al (2004) Containing a haemorrhagic fever epidemic: the Ebola experience in Uganda (October 2000–January 2001). Int J Infect Dis 8:27–37

Meydani M (1992) Modulation of the platelet thromboxane A2 and aortic prostacyclin synthesis by dietary selenium and vitamin E. Biol Trace Elem Res 33:79–86. doi:10.1007/BF02783995

Muyembe-Tamfum JJ, Mulangu S, Masumu J et al (2012) Ebola virus outbreaks in Africa: past and present. Onderstepoort J Vet Res 79:451

Nathues H, Boehne I, Grosse Beilage T et al (2010) Peracute selenium toxicosis followed by sudden death in growing and finishing pigs. Can Vet J 51:515–518

Nutrition C For FS and a constituent updates—FDA issues proposed rule to add selenium to list of required nutrients for infant formula

Nogueira CW, Rocha JBT (2011) Toxicology and pharmacology of selenium: emphasis on synthetic organoselenium compounds. Arch Toxicol 85:1313–1359. doi:10.1007/s00204-011-0720-3

Oldfield JE (1999) Selenium world atlas. Selenium-Tellurium Development Association, Grimbergen, Belgium

Olson OE (1986) Selenium toxicity in animals with emphasis on man. Int J Toxicol 5:45–70. doi:10.3109/10915818609140736

Perona G, Schiavon R, Guidi GC et al (1990) Selenium dependent glutathione peroxidase: a physiological regulatory system for platelet function. Thromb Haemost 64:312–318

Pigott DM, Golding N, Mylne A et al (2014) Mapping the zoonotic niche of Ebola virus disease in Africa. Elife 3:e04395. doi:10.7554/eLife.04395

Ramanathan CS, Taylor EW (1997) Computational genomic analysis of hemorrhagic fever viruses. Viral selenoproteins as a potential factor in pathogenesis. Biol Trace Elem Res 56:93–106

Ramoutar R, Brumaghim J (2010) Antioxidant and anticancer properties and mechanisms of inorganic selenium, oxo-sulfur, and oxo-selenium compounds 58:1–23

Ravaglia G, Forti P, Maioli F (2000) Effect of micronutrient status on natural killer cell immune function in healthy free-living subjects aged $\geq$ 90 y. Am J Clin Nutr 71:590–598

Rayman MP (2000) The importance of selenium to human health. Lancet 356:233–241. doi:10.1016/S0140-6736(00)02490-9

Rayman MP, Stranges S (2013) Epidemiology of selenium and type 2 diabetes: can we make sense of it? Free Radic Biol Med 65:1557–1564. doi:10.1016/j.freeradbiomed.2013.04.003

Rowland J (2006) Chemicals evaluated for carcinogenic potential by the office of pesticide programs. http://www.fluoridealert.org/wp-content/pesticides/pesticides.cancer.potential.2006.pdf

Sanchez A, Trappier SAMG, Mahy BWJ et al (1996) The virion glycoproteins of Ebola viruses are encoded in two reading frames and are expressed through transcriptional editing. Proc Natl Acad Sci 93:3602–3607

Smith JB (1980) The prostanoids in hemostasis and thrombosis: a review. Am J Pathol 99:743–804

Stadlmayr B, Charrondiere UR, Addy P et al (2010) Composition of selected foods from West Africa. Food and Agriculture Organization, Rome, p 13–14

Tapiero H, Townsend D, Tew K (2003) The antioxidant role of selenium and seleno-compounds. Biomed Pharmacother 57:134–144. doi:10.1016/S0753-3322(03)00035-0

Tate WP, Poole ES, Horsfield JA et al (1995) Translational termination efficiency in both bacteria and mammals is regulated by the base following the stop codon. Biochem Cell Biol 73:1095–1103. doi:10.1139/o95-118

Taylor EW, Nadimpalli RAMG (1997) Genornic structures of viral agents in relation to the biosynthesis of selenoproteins. Biol Trace Elem Res 56:63–91

The I (2000) Health effects. Toxicol Ind Health 16:143–164. doi:10.1177/074823370001600308

Theis C, Reeder J, Giegerich R (2008) KnotInFrame: prediction of -1 ribosomal frameshift events. Nucleic Acids Res 36:6013–6020. doi:10.1093/nar/gkn578

Thomson CD (2004) Assessment of requirements for selenium and adequacy of selenium status: a review. Eur J Clin Nutr 58:391–402. doi:10.1038/sj.ejcn.1601800

Universitdl M (1994) Selenium enhances glutathione peroxidase activity and prostacyclin release in cultured human endothelial cells concurrent effects on mRNA levels. Biol Trace Element Res 46:113–123

WHO/Ebola virus disease (1978a) Ebola haemorrhagic fever in Sudan, 1976. Report of a WHO/International Study Team. Bull World Health Organ 56:247–270

WHO/Ebola virus disease (1978b) Ebola haemorrhagic fever in Zaire, 1976. Bull World Health Organ 56:271–293

WHO/Ebola virus disease (2014) World health organization. http://www.who.int/mediacentre/factsheets/fs103/en/. Accessed 31 Dec 2014

Weiss RB (1991) Ribosomal frameshifting, jumping and readthrough. Curr Opin Cell Biol 3(6):1051–1055.

Zachara BA, Gromadzińska J, Wąsowicz W, Zbróg Z (2006) Red blood cell and plasma glutathione peroxidase activities and selenium concentration in patients with chronic kidney disease : a review. Acta Biochim Pol 53:663–677

Zhang L, Wang H (2014) Forty years of the war against Ebola. J Zhejiang Univ Sci B 15:761–765. doi:10.1631/jzus.B1400222