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INFORMATION

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EDITORIAL

EBOLA IN WEST AFRICA: A CLARION CALL TO ACTION TO AVERT A GLOBAL PANDEMIC

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This special issue of the Pacific Journal of Medical Sciences focuses on the most serious infectious disease pandemic currently ravaging the populations of three West Africa countries – Sierra Leone, Liberia and Guinea. We can no longer afford to be complacent: the virulence of the Ebola virus, coupled with the frightening ease of its transmission in communities and across borders in our "Global Village", presents a real threat of a global pandemic.

This publication is in response to many requests from our undergraduate and postgraduate medical and health sciences students, as well as from academics and others. Many are overwhelmed by the tsunami wave of information about Ebola in the print, social and news media. Yet, a lot of the information circulating is contradictory, and some is just misinformation.

The objectives of this special issue are to provide some basic information about the causative agent of the current Ebola pandemic and to present the views of experts about the complexity and challenges of dealing with this highly pathogenic virus.

In March 2014, the Ministry of Health (Ministere de la Sante) of the Republic of Guinea officially informed the World Health Organization (WHO) of a rapidly evolving outbreak of Ebola Hemorrhagic fever (EHF) in forested areas of South Eastern Guinea [1, 2]. A total of 49 cases with case fatality of 59.2% were recorded as of 22 March 2014 [2]. The active role of Médecins Sans Frontières, Switzerland (MSF-CH) to treat infected patients was highlighted. The affected districts in Guinea were Guekedou, Macenta, Nzerekore and Kissidougou [2, 3]. The results of the Polymerase Chain Reaction (PCR) analysis of blood samples from seven patients carried out in the Pasteur Institute in Lyon, France, indicated that six samples were positive for Ebola virus. Sequencing of a section of the L-gene showed strong homology with the Zaire Ebolavirus species [2]. This was the confirmation of the outbreak of Ebola Virus Disease (EVD) in West Africa. The WHO later confirmed the spread of the infection to the neighboring countries, Liberia and Sierra Leone [3, 4, 6].

As part of the response to the confirmation of the outbreak and its spread to the neighboring countries, the WHO release detailed information and directives on the 4 April 2014, stating that [4]: *"…….. In coordination with national and regional authorities and technical partners, WHO has deployed experts to help assess and control the situation. Isolation facilities and a mobile laboratory have been established; infection prevention and control and clinical management guidance is being provided; and awareness and education campaigns, social mobilization, and risk communications activities are taking place throughout the affected areas". "WHO encourages countries to strengthen surveillance, including surveillance for illness compatible with EVD, and to carefully review any unusual patterns, in order to ensure identification and reporting of human infections under the "International Health Regulations-2005" (IHR 2005), and encourages countries to continue national health preparedness actions. WHO does not recommend that any travel or trade restrictions be applied with respect to this event"…….. [4]*

As stated by the Director General of WHO, the initial response to control the Ebola outbreak was not commensurate with the ferocity of the spread of the disease, especially to major cities, and the high fatality rates in the affected countries [5]. Thus, the current outbreak, with over 21,000 reported cases and over 8,500 fatalities, has been categorized as the largest and most complex Ebola outbreak since the index case of EVD was reported in 1976.

The Ebola virus (EBOV) is the causative agent of EVD or EHF that was first reported in 1976 in two simultaneous outbreaks in Nzara (Sudan) and Yambuku in Zaire, now the Democratic Republic of Congo (DRC) [7 - 10].

The Ebolavirus is in the order Mononegavirales and family Filoviridae (filovirus).

Five distinct species of Ebolavirus have been identified [4, 6, 9].

In 1976, a total of 284 cases of EVD were reported with 53% fatality in Sudan; the virus was identified as Ebola-Sudan (EBO-S or SUDV) [4, 9, 10]. In Zaire, a total of 318 cases were reported with 88% fatality; the virus was identified as Ebola-Zaire (EBO-Z or EBOV) [7 - 10]. In 1989, infected monkeys from Mindanao in the Philippines, imported into Reston, Virginia USA, were identified as the source of the Ebola infection that affected a few people in Reston, but no fatalities were reported [9 - 11]. The virus was identified as Ebola Reston (EBO-R or RESTV). In 1994, a female ethologist was infected with Ebolavirus, while performing necropsy on a dead chimpanzee from the Tai Forest in Cote d'Ivoire; the virus was identified as Ebola Cote d'Ivoire (EBO-CI or TAFV) [9, 10]. An outbreak of Ebola was reported in Bundibugyo district in Western Uganda in 2007; a total of 149 cases were confirmed by the CDC with fatality rate of 25%. The virus was identified as a new Ebola species and was named Bundibugyo ebolavirus (BEBOV or BDBV) [9 - 12].

Since 2000, several outbreaks of Ebola have been reported in Africa; these include the following [9, 10]: In Uganda EBO-S outbreak occurred in 2000 to 2001, 425 cases were

confirmed with fatality of 53%; from October 2001 to March 2002, EBO-Z outbreak occurred in Gabon (65 cases with fatality of 82%) and the Republic of Congo (57 cases with fatality of 75%); in Republic of Congo, EBO-Z outbreaks occurred from December 2002 to April 2003 (143 cases with 89% fatality) and November to December 2003 (35 cases with 83% fatality); Sudan in 2004, EBO-S outbreak with 17 cases and 41% fatality; EBO-Z outbreak in the DRC in 2007 (264 cases with 71% fatality) and from December 2008 to February 2009 (32 cases with 47% fatality); EBO-S outbreak in Uganda from June to October 2012, 11 cases with 36% fatality; in the DRC from June to November 2012, BEBOV outbreak, 36 cases with 36% fatality; in Kibaale district in Uganda, EBO-S outbreak from November 2012 to June 2013, a total of 6 cases with 50% fatality; in the DRC EBO-Z outbreak from August to November 2014, a total of 66 cases with 74% fatality [9, 10].

Three (EBO-S, EBO-Z, BEBOV) of the five species of the Ebolavirus have been associated with the major outbreaks of EVD in various countries in Africa with relatively high fatality rates [4 – 12]. Despite the repeated occurrence of Ebola outbreaks in Africa, including the current unprecedentedly large scale outbreak in West Africa, the primary source of the Ebolavirus is still elusive [4, 6]. Fruit bats are high on the list of possible natural hosts, followed by monkeys, apes and chimpanzees [4 – 8]. Some authors have indicated that pigs might also host the Ebolavirus [13, 14].

Significant progress has been made in elucidating the general and molecular structures of the EBOV [15 – 20]. The genome of the EBOV is a linear negative-sense single stranded RNA {(-) ssRNA} that is encapsulated in a Nucleocapsid (NC). The components of the NC include a Nucleoprotein (NP), Virion Protein 30 (VP30), VP35 and RNA-dependent-RNA-Polymerase (Protein L). The NC is coated in matrix layer made up of matrix proteins VP40 and VP24. This complex is enveloped in a lipid bilayer studded with the major viral Glycoprotein (GP) (Figure 1). The GP forms spikes on the viral envelope that represents the outer surface of the virion; it is involved in the attachment and entry of the virus into the host cell. VP24 and VP40 are the matrix proteins; they play crucial role in maintaining the shape of the virion and are involved in viral reproduction. NP is part of a spiral structure that includes the ssRNA in the center of the virion; VP35 is a minor protein that acts against interferon, which is the natural protein in animal cells that normally functions to destroy viruses. Other virion proteins include VP30, the Transcription activator that triggers Transcription; RNA-dependent-RNA-Polymerase (Protein L) assembles copies of the virion RNA genetic material from positive copies of RNA and transcribes them into messenger RNA in preparation for translation in the host cells.

The EBOV genome, which is about 19 kb in length, encodes seven open reading frames

(ORF) and produces 8 major gene products that have multiple functions [15 – 20]. The diagram in Figure 2 shows the order of the genes in the genome. There are 3 overlaps of genes: the first overlap is between VP35 and VP40; the second is between GP and VP30; and the third – between VP24 and L. The overlaps are limited to the conserved sequence determined for the Transcriptional signals. Three non-coding sequences are located between VP30 and VP24. The EBOV genome organization can also be represented as:

3'OH-{Leader-untranslated}-{core}-{envelope}-{polymerase}-{Trailer-untranslated}-5'OH.

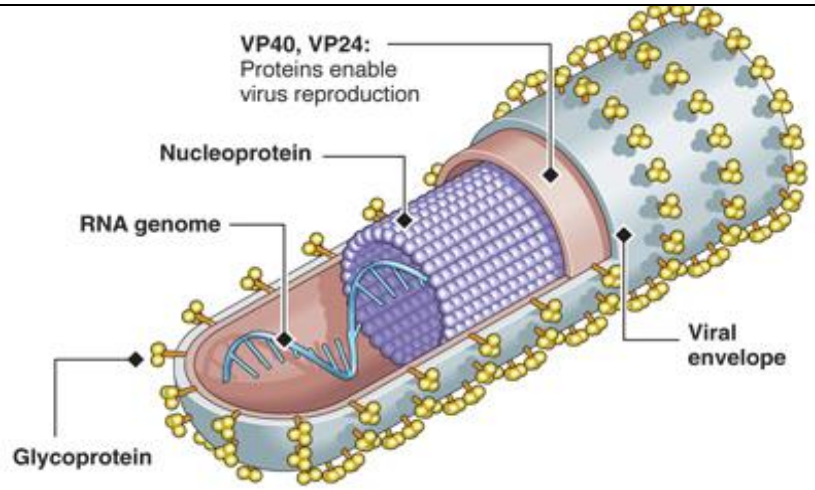

Figure 1: Schematic diagram showing the layers on Ebola virus. (Outermost viral envelope is lipid bilayer acquired from the host cell as the new virus buds off from the cell) [21]
[Credit: www.oxfordhumanists.org/wp-content/uploads/2014/12/Ebola-diagram-simple-and-neat.jpg. www.torontosun.com/2014/07/30/what-you-need-to-know-about-ebola]
VP = Virion Protein

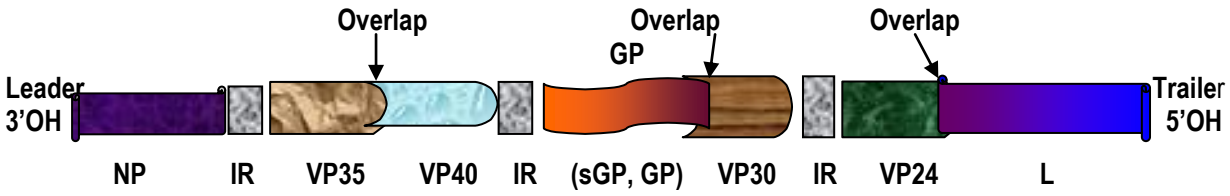

Figure 2: Relative location of genes on Negative-sense Single Stranded RNA {(-) ssRNA} linear genome of the Ebola virus [21].
(IR = Intervening Region, sGP = Soluble Glycoprotein)

Since the index case of EVD was reported about 40 years ago, no appropriate antiviral drugs or vaccines have been developed and approved [4, 6, 21, 22]. One of the major obstacles to scientific research on Ebola is the highly pathogenic nature of the virus. Scientific research work on EBOV must be conducted in high-level containment laboratory, classified as Biosafety Level 4 laboratory [4, 6, 9, 15]. By comparison, scientific research work on the Human Immunodeficiency Virus (HIV) is conducted in Biosafety Level 2 laboratory. Therefore, adequate funding for scientific research on the EBOV is difficult to obtain, which constitutes another major obstacle in the development of appropriate therapy, diagnostic assays and, especially, point-of-care test kits [22].

The global impact of the current Ebola pandemic is a "Clarion call for action" from government and international agencies, philanthropists, major pharmaceutical industries and others to provide the appropriate level of funding required to produce the urgently needed antiviral therapeutics and vaccines to manage the current outbreak and forestall an even more devastating Ebola pandemic. This is significant because the geographical spread of fruit bats is not limited to the African continent; it includes Asia, Australia and America [23, 24].

I wish, on behalf of the Editorial Board of the PJMS, to thank all the distinguished authors that have contributed to the success of this issue by submitting their papers for publication. Our special thanks go to Dr. Ada Igonoh for the paper "Post Ebola Syndrome", which is our lead paper in this issue. Dr. Igonoh tells a personal story and raised several questions that need urgent attention by researchers in the medical and social sciences.

We welcome all constructive comments on the papers published in this issue and invite more papers on the Ebola virus and Ebola Virus Disease to be submitted for publication in other issues of this journal.

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POST EBOLA SYNDROME

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In the midst of the Ebola Virus Disease (EVD) outbreak in West Africa, while the attention is solely on Ebola disease patients, there is a growing group of people that are being forgotten --- the survivors (those that have recovered from the EVD). Life after leaving the isolation ward is laden with a lot of surprises that few Ebola survivors talk about. There is a culture of mutism among survivors, which may be due to their own personal quests for privacy and avoidance of stigmatization and discrimination, but for most, due to pressure from family members not to tell their stories for fear of stigmatization.

I desperately sought for accounts of survivors while I was in isolation. That was how I realized how scarce they were. I read a few accounts that talked about having persistent symptoms even several years after being certified Ebola free. I realized that there is a "Post Ebola Syndrome" that many do not talk about, but suffer privately with no one to share their woes with.

I was discharged from the ward with residual joint and muscle pains which I ignorantly attributed to sleeping on the very thin mattress that was provided in the isolation ward. The joint pains persisted for about 3 months, usually moderate to severe in intensity, unprovoked and migrating from one joint to another. I could wake up one morning and discover a swollen right knee joint which made movement around that joint very painful, oftentimes resulting in a limp and inability to even climb a staircase with ease. The knees, hip joints and shoulder joints were severely affected. Occasionally, I would experience excruciating pain in my wrists or proximal interphalangeal joints. The pains were self-limiting and usually relieved by analgesics.

Many survivors of the previous outbreaks had complained of persistent joint pains up to 7 years after recovery. I had read that survivors suffered from chronic inflammatory complications such as arthritis, but it was not certain why some developed it and others did not. The inflammatory complication is most likely as a result of immunological overdrive which was initiated during the acute infection.

I also experienced chest and muscle pains which subsided only after about 2 months after discharge.

Immediately after my discharge from the ward, I observed fatigue and generalized body weakness which was usually provoked by exertion from attempts at trying to resume daily activities that I used to engage in before I fell ill with the Ebola Virus infection. Activities such as walking to the grocery stores just down the street resulted in dyspnea and fatigue which were relieved by complete bed rest for a day or two. My body somehow found a way to tell when I was exerting myself more that I should and I learned to listen.

Survivors struggle with anorexia and usually only regain their normal healthy appetite after several weeks in recovery. This perhaps may explain why weight gain is difficult during the first few weeks of recovery. Nutrition must be optimum and supplemented with essential vitamins and minerals to aid the body recovery.

Shortly after I was certified Ebola free, I noticed widespread generalized desquamation of my skin especially on the arms, elbows, hands, abdomen and feet. No amount of exfoliation could completely get rid of the scaly patches. The desquamation was of course embarrassing but after one month, it began to subside, although it persisted on the medial aspects of my feet. I studied the feet of other survivors and noted that we all had patches of scaly skin on the medial aspects of our feet. *Could this be a side effect of the heavy disinfection that characterizes the treatment process?*

My hair was often admired by women who wanted to know my routine. Sadly, 2 weeks down the road to recovery, I noticed clumps of long strands of hair falling off my comb, even from barely touching the hair. The hair was not experiencing breakage, but was literally falling off from the roots. The hair loss was generalized but seemed to be more on the frontal part of the scalp. In addition to the hair loss, I observed that the texture of my hair had changed from being curly and coarse to straight and thin. I eventually cut my hair to hide the embarrassment. Incidentally, I had read about hair loss in some EVD survivors while I was in isolation and hoped that I wouldn't suffer the same fate, but I did. Still, it is only hair and, as sure as I have breath, hair can grow again.

Some survivors complain of progressive visual loss with a few going completely blind afterwards.

It is said that chronic uveitis is also a long term complication of the EVD, though the mechanism is unclear. There are some who complain of tinnitus, progressive hearing loss and even balance related problems.

In addition to the physical debilitation of Ebola survivors, they are faced with varying degrees of psychological issues. Some continue to suffer depression, while others experience feelings of guilt, having survived when others died. Post-traumatic stress disorder (PTSD) is often experienced by survivors who suffer from insomnia weeks after discharge and cannot seem to "move on" with their lives. It is now six months after discharge and my symptoms have greatly subsided but the questions still remain unanswered. *What is responsible for these complications? Is it the Ebola virus itself, the treatment or the heavy disinfection?*

There is an urgent need to identify these complications, and better understand them in order to stop their progression. Scientists and researchers need to conduct longitudinal studies to understand what their root causes are and if there is reversible or irreversible organ damage years down the line. No two survivors are the same, with some having it worse than others. There is therefore a need for Ebola survivors to be closely followed up by psychologists and physicians for at least one year after discharge.

Ebola survivors should not have to be reminded of what it is like to have Ebola virus disease for the rest of their lives. Visual and hearing loss can be halted and reversed and we can raise networks of Ebola survivors who can enjoy rather than endure the second chance at life that they have been given.

On-line links to the real story of Dr. Ada Igonoh:

- www.bellanaija.com/2014/09/15/must-read-through-the-valley-of-the-shadow-of-death-dr-ada-igonoh survived-ebola-this-is-her-story/
- www.huffingtonpost.com/2014/09/22/ada-igonoh-survivor-ebola_n_5864156.html
- www.youtube.com/watch?v=s38vC-h1-5g

EBOLA: A PUBLIC HEALTH NIGHTMARE IN WEST AFRICA, SIERRA LEONE'S CURRENT BATTLE

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Introduction:

In an October 16th 2014 publication of the New England Journal of Medicine, a startling conclusion was made, "without drastic improvements in the control measures, the numbers of cases of and deaths from Ebola Virus Disease (EVD) are expected to continue increasing from hundreds to thousands per week… [1].

Such a statement conjures memories of the movie "Contagion" in which an airborne virus leads to pandemic, responsible for numerous deaths worldwide. The EVD outbreak in West Africa, declared a "global health emergency" by the World Health Organization (WHO) in August 2014 [1], has placed an unbearable stress on the vulnerable medical infrastructures of Sierra Leone, Liberia and Guinea [2].

The personification of such stress has been in the high mortality of those responsible for the direct care of infected individuals. According to the latest WHO figures, 820 health-care workers have been infected with EVD of which 488 have died, in the three heavily affected countries [3]. In Sierra Leone, 12 physicians have lost their lives to EVD.

Understanding transmission dynamics of EVD and recognizing the earliest symptoms are keys to curbing disease transmission. A major hurdle is that EVD presents with non-specific symptoms, making it hard to differentiate from other more common regional diseases [4]. In regards to the high number of transmission in health-care workers, poor infection control infrastructure in non-Ebola Treatment Units (ETUs), lack of early recognition of symptom, non-identification of infected individuals, lack of beds in ETUs and cultural barriers have been identified as major

proponents of disease transmission and targets for decreasing transmission [1, 4].

As of January 12, 2015 the Centers for Disease Control and Prevention (CDC) USA reported a total of 21,171 cases with 13,397 having been confirmed by laboratory methods and 8,371 reported dead, in the three heavily effected countries (Figure 1). The largest number of suspected and confirmed cases (10,094 and 7766) has been reported from Sierra Leone [5].

Clinical Presentation and Transmission:

In a recent article published by Ansumana et al. fatigue, anorexia, fever, nausea/vomiting, muscle pain, joint pain and headache were the most common presenting symptoms at time of admission to their ETU in Sierra Leone [6]. These findings are similar to those reported by the WHO Ebola Response team's NEJM publication, from all three countries. They noted fever (87.1%) as the most common presenting symptom followed by fatigue (76.4%), anorexia (64.5%), vomiting (67.6%), diarrhea (65.6%) and headache (53.4%) [6]. Schieffelin et al also noted in Kenema, Sierra Leone, fever as the most common presenting symptom (89%) followed by headache, weakness and diarrhea [7]. Transmission of EVD occurs via direct contact to infected individuals or deceased person's bodily fluids or by contact with contaminated surfaces and materials [8].

A key element of identifying exposed and infected individuals (contact tracing/ case finding) as a measure of outbreak containment is that it allows for the separation of the unexposed. Allowing for observation of those suspected to have been in contact with an Ebola patient in the proper setting for 21 days and early initiation of a treatment protocol 1, 8].

Treatment in a proper ETU leads to improved outcomes, decreased transmission and decreases the risk to health-care providers. Safe burial methods, another important factor in controlling EVD transmission has also played a major role in disease control [1, 8].

Current Status and Conclusion:

Hope in the horizon is a reality. Like the fisherman lost in an unyielding storm, sees home. The Ebola crisis in Sierra Leone, Liberia and Guinea shows signs of relenting its unyielding choke hold on these countries. Ansumana et al. recently reported a decreased in case fatality from 47.7% to 31.7% within the same facility in Hasitngs in Sierra Leone. This is also a decrease from the 74% case fatality reported by Schieffelin et al. at the Kenema Government Hospital in Sierra Leone. Comparing new confirmed cases in Sierra Leone from the last 21 days and the last 7 days up to the 11th of January 2015, a rapid decline was noted (Figure 2) [9]. There has also been a fourfold decrease (426 to 108 cases) in the number of cases reported in the Western (urban and rural) areas in Sierra Leone, within the same period [9]. In Port Loko and Kono districts in Sierra Leone, significant decreases (3 fold and 5 fold) have also been reported with other major areas reporting zero new cases.

Although transmission of EVD is yet to be fully controlled and eradicated from the region, we must applaud the efforts of those who have

sacrificed their lives and continue to put their lives at risk to control this pandemic. The projected thousands of weekly cases have been quelled to a manageable number. Case identification, contact tracing, preventive and treatment measures, community involvement and proper burial procedures have proven to be effective public health tools in the control of EVD.

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Figure 1: 2014 Ebola outbreak in West Africa: Outbreak distribution map, showing the three heavily affected countries [5]: www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html

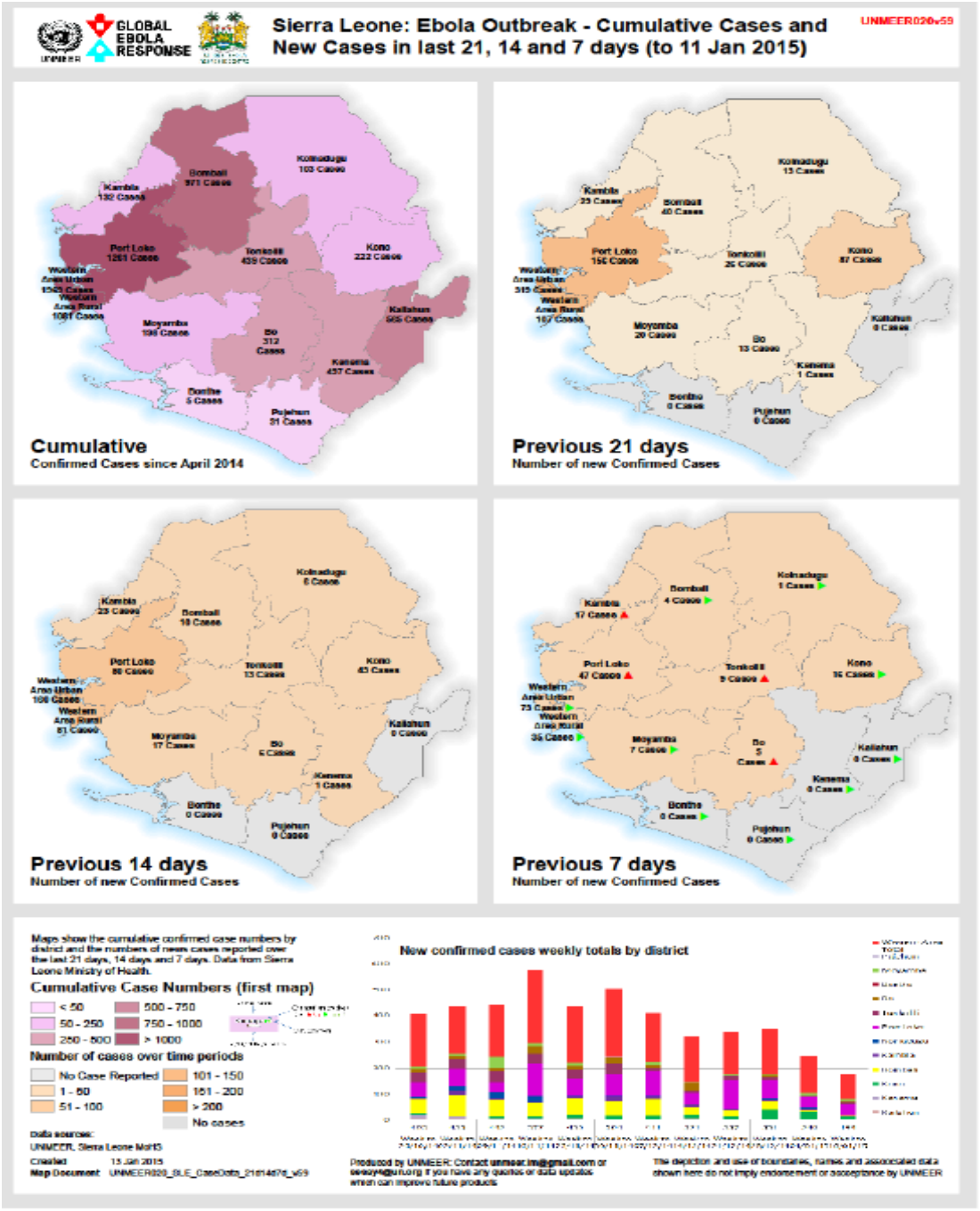

Figure 2: Sierra Leone: Ebola outbreak – cumulative cases and new cases in the last 21, 14 and 7 days (to 11 January 2015) [9]: http://nerc.sl/www/sites/default/files/UNMEER020_SLE_CaseData_21d14d7d_v59.pdf

RE-EMERGENCE OF EBOLA VIRAL INFECTION IN WEST AFRICA

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The epidemic and pandemic outbreaks of infectious diseases is not a new phenomenon in the history of man. The bubonic plague in the 14th Century that ravaged several parts of Europe and Asia is one such example, and so also the highly contagious Influenza viral outbreak in the early part of the 20th Century. Man is still battling with the scourge of AIDS. The perennial concern especially in the tropical African countries has been the emerging and re-emerging zoonotic infectious diseases such as Lassa fever, Marburg viral disease, Chikungunya and the deadly Ebola viral disease (EVD) that surfaced again in West Africa in early 2014.

The Ebola virus is an RNA virus belonging to the Family Filoviridae and genus Ebolavirus. There are five genetically distinct strains in the Family, named after the countries of identification: Zaire type (ZEBOV); Sudan (SEBOV); Cote-d'Ivoire (CEBOV); Bundibugyo (BEBOV) and Reston (REBOV). ZEBOV is recognized as the deadliest, first identified in 1976, along with the SEBOV about the same time [1]. REBOV has been identified as causing disease only in non-human primates. Other outbreaks had occurred between 1980 and 1993 including Gabon, Uganda and Ivory Coast; and now having the current outbreaks in the West African sub-region. It is believed that the Ebola virus (EBOV) was most likely transmitted initially from animals such as bats and non-human primates through hunting and collection of sick or dead wild animals, as well as during handling or consumption of uncooked bush meat - a practice that is rampant in African countries especially in the rural areas [1]. The fruit bats are a popular source of forest meat for humans and are prepared by hand, to be dried, smoked and \or cooked. Handling or consumption of forest fruits contaminated with bat saliva or faeces is also a possible mode of

transmission. The disruption of the ecosystem resulting from extensive afforestation, and economic activities such as hunting might have provided direct as well as indirect contact between humans and natural reservoir of the EBOV. There have also been reports of a high prevalence of EBOV antibodies in humans in some areas of the affected communities of Central Africa, without any history of a previous outbreak. This is believed might be an outcome of exposure to yet unknown less pathogenic or non-pathogenic variants of the EBOV. Field studies and epidemiological surveys have also demonstrated the absence of clinical signs in the fruit bats that are known to be the natural reservoir hosts of the virus [1].

Essentially Ebola is a zoonotic, with human transmission that is responsible for epidemic outbreaks occurring through bodily contacts, or indirectly with contaminated surfaces. Fortunately no transmission is yet associated with air or water, although the possibility of a mutated strain having such characteristics has been highlighted. EBOV spreading through the air under carefully controlled laboratory conditions has been demonstrated [2]. However, no such transmission has been linked to humans, for the implication of that – globally is frightening. There is the need, therefore, to contain the current epidemic and limit its geographical spread. The world community is aware of this and is responding fairly well, for the on-going Ebola epidemic far surpasses the total number of all previous outbreaks combined [3]. It is not only an African problem; it's potentially a global world problem, as communities are linked together by land air and sea. The current outbreak started in early 2014 in Guinea and has spread to neighbouring countries, thereby becoming the largest Ebola outbreak in history and the first of its kind in West Africa [3]. Unfortunately EBOV infection may mimic many other tropical diseases such as malaria, typhoid, more so at its initial phase of presentation. As a result of the rarity of the EVD in most parts of Africa, laboratory investigations are usually oriented towards the more common endemic pathogens in those areas. Yet early laboratory confirmation of suspected cases is essential to implement appropriate control measures. As a class-4 pathogen, EBOV culture requires a maximum containment facility, which is beyond the reach of most of the affected countries. The affected as well as the vulnerable countries in Africa have dysfunctional health care system a consequence of fragile political and socioeconomic situations. A case in point is that of Liberia and Sierra Leone, countries that had emerged not long ago from bloody civil wars, with near collapse of infrastructure and economic activities. Unfortunately the much needed educated professionals have migrated out.

The human body response to EBOV involves both the inflammatory as well as the adaptive systems. Unlike the other enveloped viruses, EBOV does not exhibit any high degree of

variability in its attempt to evade the host immunity. The most important weapons of the EBOV are its Glycoprotein (GP) and the VP35 components which cause the alteration of the target cell function resulting in cytotoxic effects on macrophages and the endothelial cell function [4]. This disrupts inflammatory cell function and the integrity of the vasculature. The VP35 goes to the extent of binding to the RNA thereby hiding it from the innate immune system preventing the body from producing the immune signaling molecules known as interferons, which normally help attract and induce specialized immune cells to boost its adaptive immune response.

The main objective of treatment is to provide an optimal care to the patient with maximum protection of the medical and the nursing staff. EBOV is a potential biological weapon, and therefore of utmost and urgent importance to develop a candidate vaccine that confers interspecies cross-protection against the various species. So also is the need to develop and make available to the community effective antiviral drugs for therapeutic purpose. Currently, there is no available specific therapy with demonstrable efficacy in the treatment of Ebola infection, especially the Ebola haemorrhagic fever (EHF), and there are no commercially available vaccines. A recombinant human monoclonal antibody directed against the envelop GP of the EBOV has been shown to possess neutralizing activity [5]. Such may be useful in vaccine production or as a passive prophylactic against the virus. There are several trials ongoing concurrently and in different countries. Hopefully by the middle of 2015 the conquest of EBOLA will be over.

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EBOLA – NOT JUST ANOTHER EPIDEMIC

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INTRODUCTION:

The world has seen many epidemics before, but none quite compare to the current outbreak of Ebola Virus Disease (EVD) also known as Ebola Haemorrhagic Fever (EHF) that began in Guinea in West Africa in December 2013, was declared an epidemic by the World Health Organization (WHO) in March 2014 [1] and then spread first to the West African states of Liberia, Sierra Leone and Nigeria and later beyond to Europe and America. According to the WHO Situation Report of 14 January 2015, a total of 21,262 people have been affected and 8,414 of them have died [2]. WHO considers these figures an underestimate as cases and deaths continue to be under-reported.

This is not the first Ebola outbreak in history. There have been several outbreaks since the one in 1976 near the Ebola River in the Democratic Republic of Congo (DRC) [3, 4, 5] that gave the disease its name, but the current one is by far the worst ever [6]. Already, it has caused more deaths than all the previous Ebola epidemics combined [6] and shows no sign of abating yet.

The horror of EVD that has also contributed to its spread is that the epidemic is not only a biological disease, but also a psycho-social, cultural, political and economic tragedy.

Biologically, Ebola virus (EBOV) is a single-stranded RNA virus of the Filoviridae family and genus Ebolavirus, which has five different species [7, 8]. The particular species responsible

for the current outbreak is the Zaire strain [7, 8]. The EBOV replicates inside the human host and the greater the replication in the patient the more lethal the infection. Left untreated, the mortality rate can be between 50-90% [7]. With treatment, which can only be supportive as there is no specific treatment for EVD, the mortality rate may be lowered to between 30-50%. That is still an extremely high death rate.

Transmission:

Transmission is generally human to human, via direct contact. EBOV is transmitted through the skin and body fluids such as urine, saliva, sweat, faeces, vomit, breast milk, tears, semen and vaginal fluid [7]. People with the virus can only infect others after they develop symptoms [7], that is, when the viral load is high. Asymptomatic patients, although they have the virus, do not transmit it. People can also contract EBOV via inanimate objects like needles, syringes, razor blades, bed linen and clothes that have been contaminated with the virus from an infected person [7].

According to the Centers for Disease Control and Prevention (CDC), not only can EBOV survive for several days at room temperature in body fluids such as blood, but it can also survive for several hours on dry surfaces such as door knobs and countertops [9]. People can therefore be unwittingly infected via touching these dry communal surfaces. EVD is an acute illness and there is no carrier state. Those at highest risk of infection include family members of patients and health workers. Women are twice as likely to contract Ebola as men, and this is thought to be due to the fact that women are the usual caregivers and nurses of sick family members.

Signs and symptoms:

EBOV has an incubation period of 2-21 days. Fever is usually the first symptom and precedes the contagious stage. Other symptoms include severe headache, muscle pain, weakness, fatigue, diarrhoea, vomiting, abdominal pain, unexplained bleeding or bruising and in some cases delirium and seizures [9, 10]. People infected with EBOV are not infectious till they become symptomatic.

A Person Under- Investigation (PUI) is defined by CDC as one who has signs and symptoms of EVD as well as risk factors for EBOV infection within 21 days before the onset of symptoms [10]. Risk factors include history of travel to, or residence in, countries with high prevalence of EVD, contact with a person known to have or suspected of having EVD either by direct contact or indirectly via their body fluids or contaminated fomites, participation in funeral and burial rituals of a known or suspected Ebola victim or recent contact with non-human primates from the high risk countries [7]. A Confirmed Case is a person with laboratory confirmation of EVD [10].

Pathogenesis:

EBOV can enter the body via the mucous membrane, breaks in the skin or parenterally [7,8,9]. The virus attacks multiple cell types including monocytes, macrophages, dendritic cells, endothelial cells, fibroblasts, hepatocytes and adrenal cortical cells. The virus then migrates to the regional lymph nodes and from there to the liver, spleen and adrenal gland. Lymphocytes, though not infected directly by the virus, undergo apoptosis, resulting in low lymphocyte counts. Necrosis of the liver cells results in coagulopathy due to dysregulation of clotting factors. Necrosis of adrenal cortical cells results in reduced steroid production. Release of cytokines leads to vascular leak and impaired clotting, which in turn leads to shock and multi-organ failure [11].

Laboratory findings may include proteinuria, leukopenia with lymphopenia, reduced platelet count, elevated hepatic transaminases (ALT and AST), prolonged prothrombin and partial thromoboplastin times, and elevated fibrin degradation products [12].

Treatment / Management:

Management of EVD involves identification of cases, isolation and treatment of patients, informing the public health authorities and educating the public. Public health officials need to be notified about all EVD cases so that they can initiate contact tracing. A single patient can have between six and twenty-one contacts, some of whom will contract the disease and possibly spread it on before succumbing to it. There is no vaccine against the EBOV. There is no specific anti-viral treatment for EVD. Treatment of patients with EVD is therefore only supportive and symptomatic, aimed at combating the electrolyte imbalance, the haemorrhage, the septic shock, the Disseminated Intravascular Coagulopathy, the hypoxia and the multi-organ failure. Treatment is also focused on pain control, nutritional support, fever control, rehydration and treatment of any secondary bacterial infection [7, 13]. Most patients may die and survivors are the exception, rather than the rule. This fact has grave practical, psychological/emotional and social implications for the public, with fear being a strong driving factor.

The WHO strongly recommends patients with EVD be taken to hospital, rather than having the family attempt to nurse them at home [14]. The WHO recommendations are sound, but may pose difficulties for some families. Not all health facilities have appropriate means of transportation such as dedicated ambulances or motorcycles to fetch the sick and due to the fear of Ebola in the community, public transportation may not be available, that is, the drivers may refuse to transport the sick and their relatives to hospital. When fear of contagion results in difficulty accessing hospital care, families are left in the distressing situation of having an infectious member whom no one wants to take to hospital

and who will also put the other members at increasing risk, since his infectivity increases as his health status declines. Should the family opt to transport the patient informally by private car, the inevitable close proximity and direct contact involved in handling and transporting the patient increases the helpers' risk of contracting the EBOV.

Preventive Measures:

Advice for self-protection given to people travelling to countries where there is an outbreak of EVD (but which is equally applicable to uninfected people resident in these countries) usually includes some or all of the following:

- Avoid contact with the blood and body fluids of any person, particularly someone who is sick,
- Do not handle items that may have come into contact with an infected person's blood or body fluids,
- Do not touch the body of someone who has died of EVD,
- Avoid funeral or burial rites that require handling the body of someone who has died from EVD,
- Avoid facilities where EVD patients are being treated,
- Seek medical care immediately if you develop signs and symptoms that could be indicative of EVD,
- Limit your contact with other people until and when you go to the doctor.

Should the patient remain at home, WHO recommends separating the sick person from the rest of the family, obtaining and using protective clothing and limiting contact to prevent further infection [14].

On the one hand, the more sick the patient is, the higher the viral load and the more infectious the patient. On the other hand, the more sick the patient is, the greater his need for care and comfort from his family. Unfortunately, this is the very time the family would do well to avoid contact with him, due to his increased infectivity. The patient is therefore more likely to be abandoned during his greatest time of need. In other words, to keep yourself safe at home, what EVD demands is this: "If your family member becomes sick with Ebola, and you do not have hospital-type protective gear (which most people will not have at home) then avoid contact with the sick family member, that is, do not touch their skin or their bed linen; do not hug them (skin contact); do not wipe their sweat with your hands or touch towels they have wiped their skin with; do not wipe their tears. As your family member gets worse, they become more infectious, so you must avoid contact with them even more, despite this being the time they need their family most. Because most people with EVD are likely to die, your family member is likely to die – and so will

you, unless you isolate and avoid them as demanded above."

Psychosocially, EVD goes against human nature in a manner other lethal epidemics do not. Cholera, for instance, is readily preventable by maintaining strict hygiene during outbreaks. It does not go against human nature to wash hands regularly, boil drinking water, and avoid contamination. HIV (human immunodeficiency virus) is infectious but again, it does not go against human nature to be faithful to one sexual partner or use condoms to avoid infection. EVD on the other hand, demands what can be perceived as shunning and abandoning a loved one in his hour of greatest need. Although necessary for survival, such measures go against natural, instinctive, compassionate human behaviour.

Not only is EVD a risk during life, but sadly, the EBOV does not die immediately the patient does. The corpse is still highly infectious. The tragedy of EVD therefore reaches beyond the patient's death. EBOV endangers the family during the initial stage of illness, endangers the health workers during hospitalization and finally endangers mourners after death. Funerals are a significant factor in spreading Ebola infection, with at least 20% of new infections occurring during funerals of EVD victims [15]. Funerals occur in a socio-cultural context. People wash bodies before burial. People dress bodies before burial. People touch bodies before burial. All these pose risks. Those most at risk of contracting the EBOV during the funeral are the mourners who come in direct contact with the body, which remains very infectious, even after death. This contact may occur through washing and preparing the body for burial (which involves only a few mourners) or through touching the dead body as a gesture of farewell or grief (which could involve hundreds of mourners, depending on the stature of the deceased and the esteem in which he was held). WHO recommends paying respect to the dead from at least one metre away, without touching, but that distance means the mourner may not be able to clearly see the body, especially the face; so many mourners may ignore the life-saving advice.

Mourners are also placed at risk when they touch, hug, kiss or embrace those family members who nursed the EVD patient and who may have contracted the EBOV prior to death. WHO recommends immediate burial, with the body being handled by people wearing personal protective clothing and gloves. However, many victims continue to be buried by family according to normal funeral rituals, which may last for days. The incubation period of 2-21 days, coupled with the frequent delay in burying the victims, especially among non-Muslim communities, means that the funeral is often held during the very period when the dead victim's contacts start showing the symptoms, thus putting the mourners at great risk of further infection, since it is the symptomatic contacts that are infectious.

Cremation, which has been suggested in some quarters as a safer form of disposal of infected bodies, is culturally abhorrent to many communities. Even where the family is willing to comply in order to protect themselves, they would still be psychologically distressed by the impact of having burnt their loved one's body to ashes and the belief that by doing so and failing to bury the body they had interfered with the passage of the spirit to the next world. A funeral offers family members and other mourners a final chance to pay respects to, and send off, the dead person. Funeral customs also offer solace to the bereaved as others share their pain and mourning. With Ebola, the recommended way of interring a body would involve prompt burial (before all the relatives get a chance to come and say goodbye) by trained, professional handlers (denying the family the opportunity to perform what they consider their duty to the dead), during a funeral with a minimal number of mourners, no greetings or condolences that involve touch, and viewing the coffin from a distance of at least one metre (leaving mourners feeling they had neither attended a proper funeral nor condoled adequately with the bereaved). Any symptomatic family members would also be required to be kept at least one metre away from other people, a pariah situation that can only add to their grief.

Other customs such as distributing the clothes the deceased wore, if carried out soon after death, could potentially spread the virus, albeit to a much lesser extent than direct contact with the body.

A few cases have been traced to a custom of rinsing children with water that had been used to wash the body of a traditional healer in the belief that the healer's wisdom and abilities would be passed on to these children. This custom, which would have been innocuous, had the healer died say of malaria or a heart attack, proved deadly to the children because the healer had died of EVD contracted from the patients who had come to the healer for treatment.

In many communities, the place of death is not the preferred place of burial, even during an epidemic such as Ebola. Families prefer to have their loved ones buried at home, on their ancestral land, even if they died in a town a hundred kilometres away. During the sometimes complicated process of repatriating the body home, there is a risk of infection at the place of death, risk during transportation and risk at the destination. Healthy mourners travelling in for the funeral could also contract the virus from symptomatic family members. As such long-distance mourners tend to stay a few days and not just the day of burial, they could become infectious by the time they leave the funeral and carry the EBOV back to their usual place of residence. If this involves a lengthy journey, they could spread it along the way as well as at their final destination.

EVD control demands a change in normal social behaviour within the community, both in the

home setting and in social settings including funerals, market places and church (and worshippers tend to shake hands and hug a lot). Shaking hands, which is the commonest form of greeting, is actively discouraged in areas affected by Ebola. Hugging and kissing are likewise discouraged. With HIV, one can safely shake hands with a friend. With cholera, as long as a person washes his hands, he can continue shaking hands in greeting. With EVD, however, greeting someone by handshake or kiss could be a death sentence. People in the affected communities are therefore expected to follow a "hands-off" policy when socializing with one another. Not only is this difficult to maintain in a casual setting, but it becomes heartbreakingly hard in a family setting where there is a patient with EVD. Imagine a scenario where the patient is a feverish little child crying in pain for its mother. What parent would not instinctively reach out to wipe the sweat off the feverish face (often with their bare hand), wipe the tears and cuddle the child close? It goes against human nature to simply watch your sick child suffer from a "safe distance", which with Ebola is the correct thing to do, unless the parent has on a protective gear. If that distressed child stretches up his arms to be picked up and comforted, the uninfected mother, not having protective gear, is expected to just look at the child from at least one metre away and not touch the child. If the child crawls to the mother and tries to touch her or climb onto her knee, she should back away and maintain a safe distance, unless she wants to join that child in death. How psychologically traumatizing would that be for a parent, to deliberately ignore or avoid their child in their hour of need?

Economic impact:

The majority of patients are in the 15-44 year age group, that is, the young, productive age group. The fatal illness removes the contribution of the sick patients to the economy. Isolation of contacts means they have no access to their day to day income generating activities or food production. They cannot go to their farms or to market. Trade, including cross-border trade, may decline. Travel alerts against EVD affected countries and banning of flights to or from these countries have negative economic consequences that may exceed the direct economic consequence of the EBOV infection itself. These consequences include job losses as tourism declines and hotel occupancy rates plummet. Trade decreases, internally and across borders and prices rise. Schools and markets may close as people stay away, and even in the health facilities, some health workers may stay away due to their fear of contracting the virus from patients and then bringing it home to their families.

The World Bank reports that nearly half (46%) of the people working in Liberia at the start of the EVD crisis were no longer working by early November 2014 [16]. The self-employed have been affected the most. Half the salaried workers

are also no longer working, mainly due to their workplaces being closed because of the crisis. The economic impact has been huge, with people having less money to spend, while prices of staple foods such as rice increased. Adults cut down on their food consumption in favour of feeding their children. The rise in food prices is attributed to reduced production and reduced access caused by restricted human movement, but also to panic buying and hoarding.

The World Bank estimates that if the present rate of transmission of the EBOV continues, the gross domestic product (GDP) of the three countries most affected, Guinea, Liberia and Sierra Leone, could decline by between 3.7 and 7.3 percentage points [16]. As confidence falls, exchange rates also become volatile, due in part to capital flight.

Fear:

It is the main psychological complication of this epidemic and it includes fear of the illness itself, but also fear of isolation, fear of social rejection (stigma), fear of the hospital and fear of going about one's day to day public activities. Fear, and attempts to overcome it, can exacerbate an already serious epidemic.

Fear of the illness:

EVD is lethal, currently it has no cure. EVD is highly contagious, in life and also in death. As a result, it creates fear and despondency even among non-cases. Among health workers, who as a group are disproportionately victims of Ebola compared to the general public, the fear is that they may contract the illness and die a quick, painful death isolated from their loved ones, some of whom they might even had infected before being isolated. The public too is terrified of Ebola, the rationale being that if even doctors and nurses are dying, and in such disproportionately high numbers, what chance would members of the public have? Within local communities, distant communities, neighbouring countries and even countries overseas, fear of EVD has gripped people and shaped their behaviour to an extent that far outweighs the actual threat of the disease.

Isolation and quarantine:

Isolation is a key component of the management of the EVD epidemic. However, isolation and fear of isolation come with psychological and political consequences. At times, involuntary isolation and quarantine has had to be enforced by armed government forces like the police or even the military. This has been viewed negatively by some communities in areas that were once battlefields, and where the sight of armed soldiers evoked unwelcome memories of past horrors, as in some parts of Liberia and Sierra Leone. Soldiers, unlike health personnel, are associated with violence and war, not with health care. Politics has not been spared either. Communities perceived as opposition strongholds are less likely to trust and comply with the ruling government's efforts to institute

measures to control the spread of the EVD. Being quarantined and having their movements restricted could be seen as a political ploy, rather than the public health issue it is. Lack of trust in the government and suspicions about the government's true intentions in enforcing quarantine also contribute to people trying to avoid quarantine by not reporting cases of EVD. The same suspicions also lead to those already quarantined trying to break out and flee to the perceived safety of their communities, and possibly carrying the virus with them as they flee. Fear of quarantine may also deter health seeking behaviour. Nobody would like to be "locked up" for the requisite 21 days away from their friends, family, community and workplace.

Fear of Stigmatization:

Panic, fear and paranoia are triggered among the healthy as well as the EVD patients. There is fear of being stigmatized and treated as outcasts, which could delay seeking health care. Even after recovery, survivors may be viewed with suspicion and kept at arm's length by the community when they return home. Health workers are not spared the stigma, either, as demonstrated by the negative reaction shown towards some American volunteer health workers returning from Liberia and Sierra Leone to their homes in the US, with suggestions from some quarters that they should be kept in isolation for 21 days prior to entry into their country, due to their possible exposure to the EBOV.

Fear of the hospital:

WHO advises people not to care for patients at home but to seek treatment in hospitals where there are health staff and equipment necessary to manage EVD [14]. But people have developed a fear of the hospital. There may be reluctance on the part of patients with EVD to go to hospital due to fear of never being discharged, since most of the patients may die. This is compounded by the fear of the patients never seeing the family again before they die, since visiting is discouraged. Because of the lethality of the disease the community may view admission to hospital as admission to death and avoid getting admitted. Families may conceal a member's illness, keeping him at home and caring for him without protective wear, and thus risking the lives of the other family members, especially the main carer. People with EVD-like symptoms may not wish to go to hospital, since suspected EVD cases often share ward space with confirmed cases. There is therefore understandable fear of contracting the illness there, if one did not already have it. Fear of contracting EVD from the hospital may result in patients suffering from other illnesses refusing to seek help, be this for malaria, typhoid, meningitis or other serious but treatable illnesses. The use of dedicated staff in hospital, where available, is helpful in reducing the risk of staff transmitting the infection from the patients with EVD to other patients, but not all health facilities have sufficient numbers of such

staff. Other patients and their families may therefore be afraid to be attended to by doctors and nurses who have treated EVD patients. When hospitals have admitted and confirmed EVD cases, other patients in the hospitals have been known to flee, as their fear of contracting EBOV overrides their concern about the illness they were seeking help for.

EVD may also result in increased morbidity or mortality from other illnesses. When significant bed space and health personnel are diverted to Ebola, what becomes of those suffering from other illnesses? EVD is a quick killer. Unlike with HIV infection, a patient with EVD develops symptoms within days, needs to be isolated promptly and for the majority the trip to hospital is the last time they will ever see their home or loved ones, due to the lethality of the infection and the necessary isolation policy. Death usually occurs within two weeks of the onset of symptoms. This means the patient only has time to infect his loved ones, but not enough time to get his affairs in order and make arrangements for the care of the family. An EVD death is a sad and lonely death. Nobody holds the hand of a dying EVD patient in comfort.

The way forward:

Concerted efforts are being made to contain this EVD epidemic and save lives in the affected countries in West Africa. Some experimental drugs are on trial. Isolation policies are being implemented. Supportive and symptomatic treatments are being given. Home kits for the care of EVD patients are being freely distributed by organizations such as Medicins Sans Frontieres. However, the battle will not be won just in the health field. The epidemic has economic, social, cultural, psychological and political consequences, which must also be addressed. In addition, Fear, which strongly influences the behaviour of victims, must be allayed. This would involve huge, multi-disciplinary effort, but without it the resolution of the current crisis may be prolonged.

CONCLUSION:

The current EVD epidemic in West Africa is likely to get a lot worse before it is brought under control. This will not be because of lack of knowledge about how to control its spread, but because the means of controlling it extend beyond health measures into the realms of people's natural instincts, longstanding social behaviour and what it means to be a compassionate, caring human being in the context of the community's accepted ways of living and dying. That is why Ebola Virus Disease is not "just another epidemic."

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EBOLA! ENOUGH OF THE HYSTERIA: Letter to the Editor

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I wish to express my opinion like several others who have spoken or written about Ebola virus disease (EVD) in recent times. I am coming from a different premise. There is a Spanish proverb that says "The beginning of health is to know the disease". Ebola has been known to medical science for almost four decades [1] and precisely since 1976 when the index case appeared in Kitwit, Democratic Republic of Congo (then Zaire). Since then about 20 more epidemics have occurred, some involved Uganda, Sudan and Gabon [2-4]. We know that Ebola is a severe, often lethal and contagious viral haemorrhagic disease that can infect humans and non-human primates such as monkeys, gorillas and chimpanzees and the fruit bat, which is its intermediate host. Ebola virus (EBOV) is spread through bodily fluids like plasma, serum, saliva, sputum, semen and urine. It can also be transmitted through breast milk, vomit, tears mucus and faeces. A broken skin facilitates its transmission.

The EBOV does not survive long outside the human body and transmissibility is much more by direct contact of body fluids from patients in the community. Recent reports published in American Journal of Transplantation show that the EBOV can also be transmitted through organ donation [5]. The researchers warn that it is “very important not to overreact to the very low risk that a potential donor might have the Ebola virus, and as a consequence, unnecessarily discard potentially life-saving organs” [5]. The EVD symptoms include fever, headache, muscle pain, vomiting, cough, diarrhea, stomach ache, kidney

and liver diseases, weakness, difficulty in breathing and bleeding into the skin and other organs and also vesicular rash or rose spots or even inflammation of the throat [6].

Virologists and epidemiologists have told us that Ebola is caused by a zoonotic filovirus that belongs to a new taxonomic group, Filoviridae.

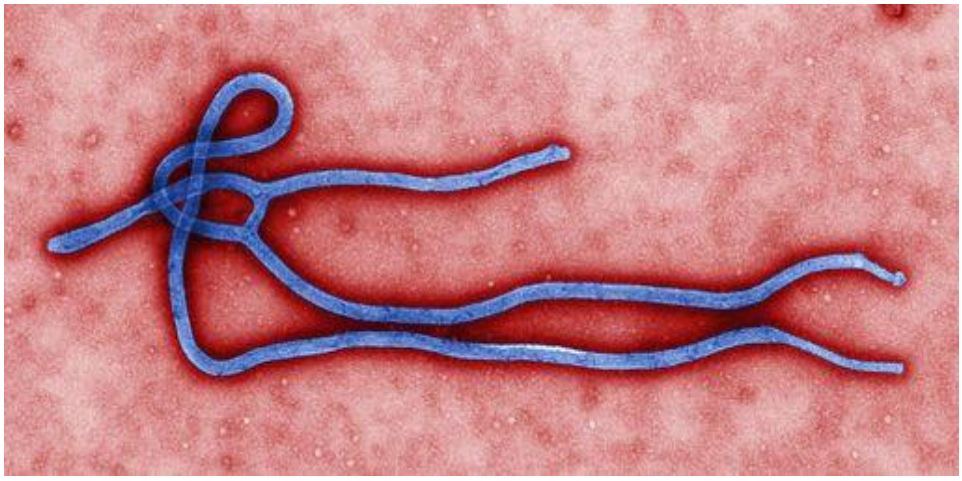

Figure 1: Ebola Virus: Credit: CDC microbiologist Cynthia Goldsmith—-Electron Micrograph [9]

Five species have so far been identified. With the exception of Reston ebolavirus, which has only shown pathogenicity among primates and Tai Forest ebolavirus, which has caused only a single human disease to date; the remaining three species (Zaire ebolavirus, Sudan ebolavirus and Bundibugyo ebolavirus) are well known for human to human transmission [7]. EBOV is a pleomorphic, single stranded RNA virus with average diameter of 80nm, but with a length that varies from 130nm to 14000 nm (Fig. 1) [8]. EBOV is a biosafety IV pathogen that has never before infected so many people so quickly over such a vast geographical region for so long that it has sparked an international health response. The EBOV is smart at suppressing host anti-viral response that allows the virus to spread quickly throughout the body. EBOV is not airborne. It can mutate during replication-when errors in its RNA may weaken its ability to cause an infection [5]. The United States Centers for Disease Control and prevention (CDC) maintains that this is not only the largest recorded Ebola outbreak in history but also the first Ebola epidemic that the entire world has ever known. The latest statistics put the number of fatality in the current outbreak in West Africa at about 8,000 with over 20,000 that may have been infected [5]. Most of these figures are from the three epicenter countries of Guinea, Liberia and Sierra Leone. Recent reports indicate that the epidemic in Liberia is beginning to slow down

with fewer new cases being reported. Unfortunately the story is different with Sierra Leone where there is a new outbreak recording some 1692 new confirmed cases as at 3rd December, 2014 [5].

With the above mentioned information it is very clear that we are not ignorant about Ebola - what causes it and how it is transmitted. Why then this excessive excitability and panic called hysteria in the United States? Why is the fear of contacting Ebola more contagious than the disease itself? The CDC Director-Dr. Tom Frieden- has repeatedly given many press conferences on Ebola, explained times without number the CDC strategy to contain the disease, as the nation's public health watchdog [9]. The CDC has designated five airports in the country and set up testing centres to screen passengers arriving in the USA for Ebola antibody. Any passenger that has fever, provided that it is not from Influenza, Malaria or Marburg disease (caused by another lethal virus in the same family as Ebola) would be tested for Ebola and if positive would be quarantined. But you don't quarantine somebody who does not have symptoms of Ebola. The case of the Maine (USA) nurse is a lesson for all. Kaci Hickox, after risking her life to attend to Ebola patients in Sierra Leone was forced to self-quarantine herself even though she did not present with any symptoms of Ebola! She hired an attorney to free her from infringement of her civil liberty and fundamental human right. The National Institute for Allergy and Infectious Diseases (NIAID) Director-Dr Anthony Fauci- corroborated and supported the actions of his colleague, Director of CDC, all in their efforts to educate and reassure the American public of their determination to prevent the spread of Ebola in the USA [10]. Dr. Frieden appeared at the US Congress to answer questions. The United States President-Barack Obama- also summoned him on Ebola control, addressed American people many times to allay their fears about Ebola. The President even appointed an Ebola Czar to coordinate surveillance of the Ebola disease in United States. He deployed some 4000 military personnel for a mission he called Operation United Assistance to contain the Ebola outbreak at its source through logistics and other support, an operation that has cost US government $360 million so far in fighting Ebola in West Africa. The President is seeking from the US Congress additional $6.2 billion to confront Ebola at its source in West Africa and secure US against any possible spread [5]. The Vice President-Joe Biden- in a TV interview with CNN did the same. The Mayor of Dallas towed the same route in enlightening the public.

Furthermore, the United Nations Secretary-General, Ban Ki moon, has also thrown his weight in his November 3, 2014 press conference in Vienna. He warns against quarantining Ebola health workers that do now show symptoms of EVD. He added that: "The best way to stop this virus is to stop the virus at its source rather than limiting and restricting the movement of people or trade." He also noted that some US state officials have imposed quarantine on health professionals returning from Ebola-

ravaged countries, but the US government opposes such measures [5].

The two nurses from Dallas Presbyterian Hospital that attended to the index and fatal case in the US - Eric Thomas Duncan from Liberia- have been treated and declared Ebola-free. In addition, two good Samaritans from the Samaritan Purse (a Christian relief and evangelism organisation) that were infected in Liberia- Dr. Kent Brantly and Nancy Writebol- have been treated with the monoclonal antibody Zmapp. They have not only recovered but even donated plasma to save other patients. A Spanish nursing assistant who recovered from Ebola was recently released from a hospital in Madrid. A Ugandan doctor has also been released from university hospital in Frankfurt after recovery. He was treated with an experimental drug called FX06 developed by scientists at Vienna General Hospital. The drug was initially designed to treat vascular problems and heart attack. This means that Ebola can be treated and can be cured. The term "cured' is used because there is no evidence that the virus will reactivate and cause disease again, even though "we have no specific therapy that targets the virus". This is according to recent research by Christopher Blaser - a Professor of virology at Mount Sinai hospital in New York and Prof. David Moore, a Professor of Infectious Diseases at the London School of Hygiene Tropical Medicine [5].

Some misinformed persons or skeptics in our society are suggesting that the US government places a travel ban for people of West Africa even when experts have advised to the contrary since this measure cannot slow down the epidemic. The experts have also advised that the best way to contain the epidemic is to stop it at the epicenter of the disease that is Liberia, Guinea and Sierra Leone. Unfortunately Canada and Australia have barred entry for citizens from the three epicenter-countries and some US politicians, dancing to the tune of what may bring a political row, have also called for a similar ban by the United States. This did not happen.

It is being rumored that some agencies no longer want nurses from Africa (mind you no more epicenter-countries) but the whole of Africa. A friend called me to tell me that a teacher from Loiusiana is being quarantined because she returned from Tanzania. Some health workers who recently returned from Nigeria were requested not to come to work until after the period of incubation of the virus which is 21 days! Mind you Nigeria was declared Ebola-free by World Health Organisation (WHO) on October, 20, 2014. This is panic measure and NOT public health measure. Public health, as defined by the American Public Health Association, promotes and protects the health of people and communities where they live, learn, work and play. Public health prevents people from getting sick or injured in the first place. It also promotes wellness by encouraging healthy behaviour [11].

A colleague of mine recently sent me an e-mail expressing how disappointed he was to learn that "the greatest and richest country in the world today cannot manage a few cases of Ebola without panic". He went further to say that this

"just exposed the very limited knowledge and extremely poor status of the US medical education on infectious disease". This could be the case if some misguided persons in the society continue to send negative and damaging signals about the efforts the US government has made and are making to contain the scourge of Ebola. The effort is centred on increasing awareness and eliminating stigmatisation.

The WHO, as part of its commitment to safety and protection of healthcare workers and patients from transmission of Ebola virus disease through contaminated droplets and fluids, has updated personal protective equipment (PPE) guidelines for health workers. More, the WHO in October constituted a high-level meeting, chaired by its Director General - Dr. Margaret Chan- on Ebola vaccine access and financing attended by many developed and developing countries of the world, pharmaceutical companies and World Bank to address the question of Ebola vaccine. In attendance in this meeting was GAVI-a public-private partnership that funds vaccine production in low- income countries.

The good news is that the first batch of experimental vaccine VSV-EBOV is now in Geneva Switzerland as recent as October 2014. The vaccine developed by Public Health Agency of Canada used the Zaire strain, which is the deadly form of the virus causing the epidemic in West Africa. The trial of this candidate vaccine which has commenced at the University Hospitals of Geneva will also be conducted in African countries (Gabon and Kenya) as early as January, 2015, if judged safe and efficacious [5].

The United States Army Medical Research Institute of Infectious Diseases has helped to conduct much of the basic research for the two experimental vaccines available, now undergoing safety testing and clinical trials at the US National Institute of Health (NIH) [6]. At the Jenner Institute of Oxford University, scientists, led by Prof. Adrian Hill, have begun testing the safety of a candidate booster vaccine, developed by Bavarian Nordic, a company based in Denmark, to find out whether it could increase immune response seen in volunteers previously vaccinated with the GSK/NIH candidate vaccine that is undergoing trial in the United States and Switzerland. The Bavarian Nordic vaccine uses the same virus gene as in GSK/NIH vaccine but in a modified vaccinia Ankara (MVA) virus. Researchers envisage that this prime-boost approach, employed previously in malaria, hepatitis C, HIV, Influenza and Tuberculosis, will generate anamnestic response which may increase immune responses substantially and offer longer-lasting protection against Ebola. With these clinical trials for Ebola vaccine now under way, and with governments and international organisations as well as manufacturers funding them, one would expect that the panic would soon be over as the problem is being addressed. However, the challenge remains in funding to scale up to commercial production and stock-piling of vaccine to ensure adequate preparation is made should another outbreak occur [5].

Encouraged by the success story of a study by Mapapa and colleagues in 1995 in Kitwit, Democratic Republic of Congo (DRC) where seven out of eight Ebola patients were successfully treated with convalescent plasma [12], WHO has reviewed and endorsed convalescent blood and plasma as having the potential in improving clinical care and reducing the unacceptably high number of deaths. Based on this observation, interest in convalescent therapy is growing and will continue even after an Ebola vaccine is produced. The first clinical trials are starting in West Africa to test whether transfusing patients with plasma or blood donated by Ebola survivors is safe and effective in reducing illness and death [6].

As I suggested in the 1990s regarding the problem of AIDS, the only vaccine now available for Ebola is Public Enlightenment. Experts worry and warn against taking advantage of drought in Ebola drugs to give patients anything that may worsen their condition. This happened in the early years of AIDS pandemic when 'everybody and their brothers became HIV/AIDS specialists. At the end of the "game" some proved to be charlatans. It is to prevent this type of scenario that the WHO team leader on experimental Ebola drugs, Martin Friede advised that "There are situations where doing nothing is actually better than doing something that is not justified" [5]. Another way of putting it is if you cannot help the patient, do not hurt them.

The scientific quest for a ready answer to a devastating epidemic, such as Ebola, could actually waste time and resources and potentially endanger lives. For example, Italian doctors are testing the anti-arrhythmia drug - Amiodarone at a treatment centre in Sierra Leone. Although the drug has some action against the EBOV in-vitro, the fear is that the concentration required for it to be effective might be unsafe in patients. The WHO Scientific and Technical Advisory Committee on Ebola Experimental Interventions would soon publish a registry, listing drugs, testing methods and results. It is hoped that this will dissuade researchers from bad science - duplicating previous efforts and trialing drugs potentially harmful to patients that they are trying to treat.

At the forefront of the global response is a medical charity called Medicins Sans Frontieres (MSF). These doctors without borders have been playing a pivotal role since the beginning of the epidemic over nine months ago - building health centres, training care staff, treating patients and even advising the United Nations on security issues. MSF treatment centres in the three countries ravaged by Ebola (Guinea, Liberia and Sierra Leone) will host clinical trials of three potential Ebola drugs planned to begin very soon. While this study is yet to begin Karpas [13] suggests that since there are no readily available and effective drugs against this lethal virus it would be reasonable to explore the use of Passive Immunotherapy (PIT) based on the reported study of Mupapa et al. during the 1995

Ebola outbreak in the DRC mentioned earlier [12]. Based on his experience with PIT in HIV/AIDS patients, Karpas suggests that plasma from people who recovered from the Ebola infection could be used to treat not only the advanced patients but also virus-infected pre-symptomatic individuals during the incubation period [14]. Hyper immune plasma can lead to the recovery of terminal patients. If given earlier, it might prevent development of Ebola disease by reducing the viral load and helping the immune system to cope with the infection [14].

The advantage PIT has over human monoclonal blocking antibodies to Ebola virus, such as Zmapp, is that it can be offered without delay. Early studies with equine immunoglobulin have already shown activity in suppressing Ebola virus viremia and delaying disease onset and death in non-human primates [15].

EVD should not be considered as another tool for discrimination and stigma. The Bible tells us that "so whoever knows the right thing to do and fails to do it, for him it is sin" (James 4:17). An English parliamentarian and philosopher, Edmund Burke put it in a different way: "All that is necessary for triumph of evil is that good men do nothing" [16]. Next to appreciating the international and private sector outpouring of support in terms of cash and commitment, the second best thing is to appeal to the international community to hearken unto the words of a literary critic and satirist, Henry Louis Mencken "For every complex problem there is an answer that is clear, simple and wrong" [17]. Discrimination on the guise of Ebola is wrong and unacceptable. It was Martin Luther King Jr- the renowned afro-american civil rights leader- who said that “The ultimate measure of a person is not where one stands in moments of comfort and convenience, but where one stands in times of challenge and controversy" [18]. Let us stand together to defeat Ebola. Let us plan and not panic any more about Ebola virus disease.

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EBOLA VIRUS DISEASE: AN OVERVIEW

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The Ebola virus (EBV) was first identified in 1976 when there were two outbreaks, one in Sudan and one in the Democratic Republic of Congo (DRC), in a village near the Ebola River [1]. EBV is a member of the virus family Filoviridae, which includes the Cuevavirus, Marburgvirus and Ebolavirus genera. Within the Ebola virus genera there are 5 species, Zaire, Bunibugyo, Sudan, Reston and Tai forest [1]. The viruses in this and other zoonotic families have emerged onto the human scene following major environmental changes such as large scale animal husbandry, extraction of natural resources, deforestation, and the use of antimicrobials [2].

The current Ebola outbreak in West Africa, caused by Ebola Zaire is the largest ever reported; beginning in early 2014 and as of the end of November 2014 known to have claimed close to 7000 lives [3]. By early January almost 21000 cases have been reported with the loss of more than 8000 lives (4).Starting in Guinea, Ebola has crossed land borders into Sierra Leone and Liberia, and on a very much smaller scale has travelled by air and sea to other African countries and to America and Europe where sensational media coverage has produced widespread fear of epidemics [5]..

Ebola is a zoonotic infection. It is believed that the primary host is the fruit bat (or possibly other bat species) but that the virus spreads to other animals such as non-human, primates, forest antelope and porcupines. The virus is transmitted to humans by close contact with blood, secretions, bodily fluids or organs of infected animals. Human to human transmission is by direct contact with blood, secretions, organs or other bodily fluids of infected people either directly or from contaminated surfaces and materials such as clothing and bedding [1].The virus is highly infectious. The incubation period is

from 2 - 21 days, and humans only become infectious when they develop symptoms. In a study of 3343 confirmed and 667 probable Ebola cases from the current epidemic researchers estimated a mean incubation period of 11.4 days with a mortality of 71.0% in those with known clinical outcome [6]. Mortality of hospitalised patients is currently reported at around 60% (4). Characteristic early symptoms are fever, fatigue, headache, sore throat and muscle pains, progressing to diarrhoea, vomiting, skin rash and impaired renal and liver function. In some, but not all cases there is internal and external bleeding (the original name of the disease was Ebola Haemorrhagic Disease). As a result of its high infectivity and its mode of spread, Ebola thrives in situations in which basic hygiene and understanding of disease spread is poor, where health services are inadequate, and in situations where local custom decrees close contact with severely ill and deceased patients. All of these factors have fuelled the current epidemic.

In the early stages Ebola presents in a similar way to other common febrile illnesses. Diagnosis requires laboratory testing (usually by PCR) and there is often delay between suspecting and confirming a diagnosis. It has recently been reported that the meantime between symptom onset and diagnosis is around five days- during which the patient is highly infectious [6]. Blood for laboratory testing is a major biohazard, and must be handled in facilities with appropriate safety level. Point of care diagnostic testing currently being developed would be likely to reduce the time from symptoms to diagnosis and the immediate application of isolation would greatly reduce the attack rate of the disease [7].

There is currently no antiviral treatment available, although trials of three treatment regimens- two with anti-viral agents and one with convalescent whole blood and plasma –were scheduled before the end of 2014 [8]. Survival rates can be improved by early focussed supportive care such as rehydration. Such care does however put the carer at major risk and requires the use of uncomfortable full personal protective equipment (face protection, clean, long sleeved gown gloves and hood. It is sobering to realise that so far of 820 health workers known to have been infected 488 have died, their deaths being attributed to shortage and improper use of personal protective equipment and lack of training [4].

There are currently no licenced Ebola vaccines, although potential vaccines are undergoing safety trials and may become available in the foreseeable future. Currently, prevention and control depends on the application of highly effective but often challenging measures. Risk reduction measures include [1]:

- reducing the risk of wildlife to human transmission by avoiding unprotected contact with potentially infected animal sources, and ensuring that meat and animal products are thoroughly cooked before consumption,

- reducing the risk of human to human transmission by stringent hand washing when caring for, or visiting any sick patients and the use of appropriate personal protective equipment when caring for Ebola patients, and outbreak control measures,
- outbreak containment by identifying and monitoring the health of contacts of a patient for 21 days, separating those who are sick form those who are asymptomatic, prompt and safe burial of the dead, and application of scrupulous hygiene measures.

Good case management, active surveillance, a good laboratory service and social mobilisation and involvement are crucial.

Is Papua New Guinea at risk of an outbreak of Ebola?

The risks of an outbreak in Papua New Guinea (PNG) are extremely small. This does not mean there is no need for preparedness but it does mean common sense should prevail. Most of the high risk West African population are at the lower end of the socioeconomic scale and unlikely to embark on long distance international air travel. Most cases reported from America and Europe have been health workers or missionaries who have been in close contact with Ebola patients. There is very little travel of people from West Africa to the South Pacific region and particularly to Papua New Guinea, so the risk of importation is minimal. It is pertinent however for health workers to be aware of Ebola and should any person recently arrived from West Africa develop the early symptoms, the Health Department should be notified immediately and appropriate measures taken.

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PATHOPHYSIOLOGY OF EBOLA VIRUS INFECTION: A REVIEW OF CURRENT LITERATURE

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ABSTRACT:
By September 2014 the Ebola outbreak in West Africa had claimed more than 2600 lives. The disease has no approved drug or vaccines and cases have been treated with experimental drugs. Supportive care is the main stay of treatment of cases. Although research into understanding the pathophysiology of the Ebola virus has been going on for years, difficulty in conducting clinical studies because of outbreaks occurring in isolated remote villages have meant that most of the current literature on the pathophysiology of Ebola virus is from animal models. The 2014 outbreak in West Africa has put a spot light on this infection. Ebola virus infection results in cell necrosis and the ensuing systemic inflammatory responses that occurs causes the clinical symptoms and death in severe cases with a case fatality rate of 50%. Ebola virus targets mainly endothelial cells and macrophages but cells from other tissues can also be infected. Immunity to Ebola virus is not well defined and poorly understood, making development of therapeutic drugs and vaccines challenging. This is a brief review of some current literature on the pathogenesis of Ebola virus.

Key words: Ebola virus, Pathogenesis, Necrosis, Endothelial cells, Chemokines, T-lymphocyte,
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INTRODUCTION:

The *Ebola virus* (EBOV) and *Marburg virus* are the two genera of the family *Filoviridae* and are among the most virulent pathogens to humans [1]. The Ebola virus disease (EVD) cause by the EBOV was first recognized in an outbreak in the village of Yambuku along the Ebola river in Zaire (now Democratic Republic of Congo (DRC)) in 1976 [2, 3]. Other EVD outbreaks have occurred in different countries in Sub-Saharan Africa after the DRC report [2, 3]. The latest outbreak occurred in early 2014 in the West African

country of Guinea, and then spread across the border to Liberia and Sierra Leone [1]. The outbreaks were confirmed by the WHO in March 2014 [1]. The mortality rate of the current 2014 outbreak has reached 70% although in previous outbreaks the mortality rates were as high as 90% [2]. The current outbreak is larger than all previous outbreaks combined [1]. Other West African countries affected in the current EVD outbreak include Nigeria, Mali, Senegal, and Cote d'ivoir. The World health authorities and governments responded to the outbreaks with assistance to the various countries affected. The WHO declared the EVD outbreak over in Senegal and Nigeria in August 29 and September 5 2014 respectively [1]. Efforts to contain the 2014 EVD outbreak in other affected countries are continuing [4, 5].

Classification and Structure of the Ebola Virus (EBOV):

The Ebola virus (EBOV) and the related Marburg virus belong to the family *Filovirus*. This family belongs to the order *Mononegavirales*, which are pleomorhic, negative sense RNA viruses whose genome organization is similar to *Paramyxsoviridae, Bornaviridae*, and *rhaboviridae* [2, 3]. The Ebola virus genus is divided into five species: EBOV (Zaire), Sudan ebolavirus (SUDV), Tai forest (Ivory Coast) ebolavirus (TAFV), Bundibugyo ebolavirus (BDBV) and Reston ebolavirus (RESTV) [1, 2]. The current outbreak in West Africa is caused by the EBOV species [1].

The EBOV genome is 19kb long with seven open reading frames coding for its structural proteins including the virion envelope glycoprotein (GP), nucleoprotein (NP) and matrix proteins VP24 and VP40 [3]. Nonstructural proteins are VP30 and VP35 and the viral polymerase [3]. Unlike the Marburg virus, the GP open reading frame of EBOV gives rise to two gene products, a soluble 60 to 70 kDa protein (sGP) and a full length 150 to 170 kDa protein that through transcriptional editing inserts into the viral membrane [3]. The GP plays a significant role in the pathogenesis of Ebola virus infection.

Pathogenesis:

Transmission of the EBOV is by contact with an infected person's skin, blood and body fluids or contact with the meat or body fluids of an infected animal [1]. There is no evidence that the virus can be transmitted via the respiratory route but animal studies show that the virus can infect rodents and non-human primates when the virus is released as small particle aerosol [1]. The EBOV has an incubation period of 14 to 21 days and infected individuals initially present with flu like symptoms of fever, myalgia and malaise [3]. As the infection progresses patients develop bleeding and coagulation abnormalities [3]. Full blood examination at this stage may show lymphopenia and neutrophilia [3]. A

comprehensive review of clinical symptoms and treatment is given by Goeijenbier et al [2].

Because of the difficulty in conducting clinical studies in outbreak conditions, much of what is known about the pathogenesis of Ebola is from animal studies. After entering the body via mucous membranes, breaks in the skin or parenterally the virus initially infects macrophages and dendritic cells [1]. The exact mechanisms of viral particle binding and entry into various cells type including endothelial cells is still being investigated, but current research suggest viral GP may play a significant role [3, 6]. After entering macrophages and dendritic cells, the virus readily replicates and releases new viral particles causing cell death and extensive tissue necrosis [1]. Rapid systemic spread then ensures by suppression of adaptive immunity [1]. Another round of replication occurs after spread of the virus to regional lymph nodes and eventually to fixed and mobile macrophages in the liver, thymus, spleen, adrenal medulla, endothelial cells and epithelial cells [1]. Extensive necrosis of the involved cells and tissues results in an inflammatory response that produces the clinical manifestations and is the cause of mortality in severe cases [1, 3]. Molecular mechanisms of the viral entry into endothelial cells are poorly understood and are also an active area of research [3].

Late state infection with EBOV results in gastrointestinal dysfunction, coagulation defects and severe systemic inflammatory response [1]. The gastrointestinal dysfunction includes vomiting and diarrhea resulting in acute volume depletion and shock [1]. It is not clear whether this is due to the infection of the gastrointestinal tract by the virus or cytokine response or both [1]. The systemic inflammatory response is caused by release of cytokines, chemokines, and other pro-inflammatory mediators from macrophages and other cells [1]. Some of the mediators identified include tumor necrosis factor (TNF)-alpha, interleukin-1beta (IL-1β), interleukin-6 (IL-6), macrophage chemotactic protein (MCP)-1 and nitric oxide (NO) [1]. This systemic response is thought to play a major role in vascular leakage and multi-organ failure [1]. The coagulation defects observed are thought to be caused indirectly by the host inflammatory response [1]. The extrinsic coagulation pathway is activated by the production of cell-surface tissue factor (TF) by virus infected macrophages and other macrophages activated by pro-inflammatory cytokines [1]. These two mechanisms activating the extrinsic coagulation pathway promote the rapid development of the coagulopathy. Other mechanisms promoting coagulopathy in EVD have also been suggested including decreased activated protein C and decreased level of plasma coagulation factors due to live injury [1].

Immunity:

Immunity to EBOV is not clearly defined. Identification of EBOV in endothelial cells, monocytes and hepatocytes using immune-histochemical techniques showed that these cells were the targets for disease progression [3]. The virus also replicates at a high rate that it overwhelms the protein synthesis machinery of infected cells and host immune responses [3]. Failure of the adaptive immune system due to impaired dendritic cell function and lymphocyte apoptosis is thought to be the mechanism how filoviruses are able to cause severe and fatal diseases [1]. Although antibodies against EBOV are readily detectable from patients who recover from the infection, serum from recovered patients did not consistently inhibit viral replication in cell cultures [3]. Survivors of EVD have been shown to have significantly higher levels of IgM responses, clearance of viral antigen and sustained T-cell cytokine responses [3]. Animal models also suggest antibodies play a role in viral clearance but the role of cellular immunity may be more significant and is yet to be elucidated [3]. Fatal cases of EVD do not have detectable levels of virus specific antibodies [3].

The role of other cytokines such as gamma interferon, alpha interferon, IL-2, IL-10 and TNF-α in immunity and pathogenesis are still being investigated [3]. Current data suggest that the damaging and protective effects of these cytokines may depend on the cytokine profile, a delicate balance between these effects and individual host specific immune response factors [3]. Mechanisms employed by EBOV to evade the host immune system include epitope masking, production of soluble glycoproteins (sGP) that act as antibody sinks and active suppression of host immune system by production of various cytokines [6, 7].

Filovirus-specific cytotoxic T-lymphocyte response can clear the virus in animal models [8]. Research to better understand the immune responses to develop a vaccine against EBOV is ongoing [3, 6, 9].

Summary:

Understanding the pathophysiology and immune response in EVD will lead to the identification of possible targets for vaccine development and clinical intervention. Current evidence shows that the virus has a cytopathic effect causing direct cell injury and death [3].

These effects are thought to be mediated by EBOV GP targeting macrophages and endothelial cell functions [3]. The ensuing systemic inflammatory response produces the clinical effects observed. Immunity to EBOV is not well defined and poorly understood making the development of a vaccine challenging [3, 6]. Currently the major treatment of a patient with EVD is supportive [2]. Although there are currently no approved therapeutic drugs or

vaccines, there are promising signs and it is an active area of research [8, 10, 11].

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THE EBOLA VIRUS

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Introduction:

Ebola virus (EBOV) belongs to the family filoviridae and has been known to cause a systemic illness with a high mortality. Its usual clinical features include sudden onset of headaches, muscle aches, sore throat, rash and bleeding manifestations. Transmission from person to person can occur both in and outside the hospital environment which may result in intermittent outbreaks of infections.

Aetiology:

The EBOV is a close relative of another virus, the Marbag virus. Both are members of the family Filoviridae. The Marbag virus has only one subtype while the Ebola virus has five, namely: the Zaire, the Sudan, the Reston, the Tai Forest (Cote d'Ivoire) and Bundibugyo subtypes [1 – 3]. The Reston and Tai Forest subtypes are not as pathogenic to humans as the other three subtypes. Both the Marbag and Ebola viruses can be isolated in a variety of cultures including the monkey kidney cells. Both viruses are stable viruses that are capable of surviving for long periods of time at room temperature. They can be destroyed by heat and lipid solvents [1 – 4].

Epidemiology:

In 1976, out of 550 patients presenting with severe haemorrhagic fever in both the Sudan and Zaire, 470 died. In both locations Ebola virus was isolated [1, 4]. The epidemics spread in both these locations from person to person close contact as well as from injections with reused needles. It was important to note that in both locations epidemics ended when strict quarantine procedures were applied [1, 4].

It was interesting to note that in 1989, numerous deaths occurred from haemorrhagic fevers

among quarantine primates in Reston Virginia, USA [1, 4]. In the Philippines and Indonesia in the same year Ebola virus (Reston strain) was isolated from the cynomolgus monkey which were kept in the quarantine facility. Four employees were infected but none died [1, 4].

In 1995, an epidemic of haemorrhagic fever occurred in Kikwit in Zaire and out of 250 clinically identified cases, 80% died [1, 4].
During the outbreak, Ebola virus was isolated from sweat glands of symptomatic patients. This suggested that contact with perspirations of patients with the virus could have facilitated the spread of the virus. It was noted in this setting that strict quarantine measures controlled the epidemic. The reservoir for this virus however is still elusive despite very extensive research. Even though the virus is known to be zoonotic, attempts to identify its natural reservoir has not been successful [1, 4].

Pathology:
Just like its relative the Marbag virus, Ebola virus is "pantropic" which means it is capable of replicating in almost all the organs of the body [1].

Clinical Features:
The incubation period of the EBOV is 3 to 9 days [1, 5, 6, 7]. The initial symptoms appear to be headache in the frontal and temporal areas, malaise, muscle aches in the lumbar area, nausea and vomiting. Fever usually ranges from 39.4 to 40 degrees Celcius. About half of the patients usually complain of conjunctivitis. In the first 3 days diarrhoea can be severe. There may be some lethargy and a change in mentation may be noted [1, 7].

Involvement of the palate, tonsil and cervical lymph nodes may be seen in the first week of the illness. On the first to the fifth day one may see a non-pruritic maculopapular rash in the face and neck which gradually spreads to the periphery. Four to five days later one may see desquamation of the rash especially on the palms and soles. From day 5 to 7 bleeding may be seen in the gastrointestinal tract, the kidneys, vagina and conjunctivae [1, 7].

During the first week the temperature remains high at about 40 degrees celcius. It starts to decrease but increases again by the 12th to fourteenth day. The other clinical signs which appear in the second week are splenomegaly and hepatomegaly, facial oedema, scrotal or labial reddening [1, 7].
Complications of the disease include orchitis which may include testicular atrophy, myocarditis with irregular pulse and electrocardiographic abnormalities and pancreatitis.

Those who die usually do so on the eighth to sixteenth day of the illness. Recovery is usually very slow during which hair loss, abdominal pain, poor appetite and prolonged psychotic disturbances may be seen. Some late sequels like transverse myelitis and uveitis have also been noted [1, 7].

Laboratory findings:

Leukopenia has been noted in the first day. Counts as low as 1000/microltre have been noted. Later atypical lymphocytes and neutrophyls may appear. Thrombocytopenia can be severe and may be seen early. Fatal cases may include disseminated intravascular coagulation. Hypoproteinaemia, proteinuria and renal failure may also be seen. A lumbar puncture is usually normal or reveals minimal pleocytosis. The erythrocyte count is usually low [1, 7].

Diagnosis:

The characteristic epidemiologic features of the virus usually help in the diagnosis. Specific diagnosis of course requires isolation of the virus. In fatal cases of filoviral infection there is a high titre of the virus but low evidence of any host immune response. Gamma irradiation is the most common way to inactivate the virus. Specialized laboratories may be able to conduct polymerase chain reaction of viral antigens [1].

Treatment:

There is no definitive treatment for the virus other than supportive care [1, 5 – 7].

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EBOLA VIRUS OUTBREAK IN WEST AFRICA: AN OVERVIEW

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INTRODUCTION:

Ebola virus (EBOV) outbreak made its first appearance in remote villages in equatorial African countries of Zaire, Sudan, Uganda and Gabon and re-emergent outbreaks have occurred in this sub region since 1976. Ebola virus appeared to be one of the deadliest global communicable diseases since onset of HIV/AIDS. It currently has no vaccine, treatment or cure akin to the latter.

Ebola virus derived its name from Ebola River proximal to the epicenter of Zaire Ebola virus outbreak, the first ever outbreak of 1976 [1-4]. Ebola virus is a zoonotic pathogen with the intermediate host or the natural reservoir thought to be bats particularly various species of fruit bats. The virus is primarily transmitted from animals to human and among humans via the body fluids [5].Ebola virus disease (EVD) is a severe and highly fatal hemorrhagic fever in human and other primates caused by four out of the five known genus Ebolavirus [1]. The genome is a negative sense single stranded RNA structure that can rapidly replicate and mutate within human host after infection [6-7]. This characteristic is feared to represent its rapid human host's adaption as it is passed among humans and likely to pose challenges to the development of a vaccine [8-9]. The Zaire Ebola virus is responsible for causing current Ebola epidemics in West African sub region, with about 21,296 suspected cases and some 8,429 confirmed deaths [10]. Its frightening mortality rate led to its being listed as a select agent; biosafety and biosecurity pathogen [11]. The scope of its spread now extend to three

continents Africa the epicenter, North America and Europe the last two by importation.

Etiology:

Zaire ebolavirus is one of the species in the genus Ebolavirus, family filoviridae order Mononegavirales [1, 12]. EBOV often causes fatal hemorrhagic fever in simian primates including human and nonhumans like great apes, with fruit bats the natural reservoir, the other implicated domestic animals are pigs and dogs [13-14]

Source:

Human activities –mining, timber operations, and deforestation from increasing human activities bring the infected wild animals (chimpanzees and gorillas) and bat species thought to be the natural reservoir of EBOV from their natural habitat of thick forests closer to man and his immediate environment. This was demonstrated in the suspected index case in the transmission epicenter Meliadou Guinea of Dec 2014, in West Africa through the 18 –month old boy. He was thought to have contracted and died from the virus few days after playing close to bat infested tree near a forest close to their settlement [15]. The transmission chain thereafter widened to his immediate family members, extended family, all that attended to the ill, burial and funeral activities in that succession contracted and died due to unprotected exposure from the mysterious disease later discovered by WHO to be the Ebola virus. Given the ease of modern transportation and global travel, the EBOV is now a risk to the entire "Global Village", with intercontinental transmission only an airplane flight away [16].

Differential Diagnosis:

A number of diseases share some of the non-specific clinical features of EVD and these were part of the challenges in early diagnosis and the containment of West Africa Ebola epidemics. EVD has been described as a flu-like syndrome at onset that can rapidly progress to full hemorrhagic fever with multi-organ failure and death

Clinically similar Marburg hemorrhagic fever was caused by Marburg virus morphologically similar to Ebola virus but immunologically distinct [17].

Diarrhea, vomiting and fever found in cholera endemic in some of the affected rural regions created confusion and delay in early diagnosis and containment of the recent outbreak.

Malaria, an endemic disease in the tropical sub region is another disease to exclude in the diagnosis of EVD as they share some of the common symptoms. Lassa fever a viral hemorrhagic disease is often encountered at the region.

Pathogenesis:

The Ebola viron requires majorly two host cell entry proteins; the cholesterol transporter protein (the host –encoded Niemann-Pick C1 (NPC1) for host cell entry and replication [18-19]. NPC1

mediates Ebola virus infection by directly binding to viral envelope glycoprotein (GP) [19-20]. The implication is that lack or mutation or modification of this protein in an individual may result in some individual resistance to the Ebola virus deadly disease. It is evidence that the NPC1 is a critical receptor mediating Ebola infection by its direct binding to the viral GP. The second lysosomal domain of NPC1 is thought to mediate the binding [21]. The second receptor is T-cell immunoglobulin and mucin domain 1 (TIM-1) [22] binding to the receptor binding domain of the EBOV glycoprotein. TIM1 is found in tissues seriously impacted by EBOV lyses- trachea, cornea and conjunctiva. As an acellular agent, viruses like Ebola virus use the combination of host and the viral encoded enzymes and host structures to produce multiple copies of themselves that eventually self-assemble viral macromolecules in the host cells [23]. Three phases of Ebolavirus infection pathogenesis have been noted [16]:

Phase I can be characterized as the transfer of EBOV from an animal carrying the virus (reservoir-bat, nonhuman primate) to a human, usually via small cutaneous breach. Similar principles apply in human-to-human transmission during Ebola outbreaks via contacts with infected blood, stool, vomitus, urine.

Phase II can be characterized as the early symptomatic stage — usually between days four and ten — where symptoms of a viral illness appear and gradually progress toward more advanced manifestations of the disease.

Finally, Phase III represents the advanced Ebolavirus disease, with hemorrhagic manifestations, impaired immunity, and end-organ failure [16]. Limited laboratory evidence indicated that pathogenesis of the disease included non-icteric hepatitis and possibly acute pancreatitis as well as disseminated intravascular coagulation [17].

EBOLA virus disease (EVD):

EVD is severe often fatal hemorrhagic fever with multi-organ failure caused by Zaire Ebola virus which is one of the 4 ebolaviruses known to cause disease in human. This has the highest case-fatality of all the ebolaviruses, average 83% since first outbreak in 26 August 1976 in Yambuku, Zaire [24]. The first recorded case was Mabalo Lokela,a 44 year old schoolteacher and the first clinical description was by Ngoy Mushola. Transmission is via body fluid through the use of unsterilized sharps like needles, close personal contact or contaminated objects.

Clinical Presentation:

Incubation period of 1-21 day, EVD begins with an influenza-like syndrome, including high fever; body temperature can be as high as 39 Celsius, fatigue, headache, joint and muscle pains, then disease soon followed by diarrhea, vomiting, chest pain, pain and dryness of the throat. There were indications of mild or subclinical Ebola

infections [25]. After 3-4 days of non-specific symptoms and signs, patients typically experienced progressively severe sore throat, maculopapular rash, and impairment of liver and renal functions, intractable retrosternal and abdominal pain, prostration, rapid deterioration to death after a mean of three days.

Hemorrhagic manifestations are common (71%) being present in half of the recovered cases and in almost all the fatal cases [25]. Bleeding from multiple sites, in some cases internal and external bleeding e.g. from gums, diarrhea with blood, haematemesis, principally the gastrointestinal tract.

The disease in human varies in severity from rapid fatality to mild illness and in some times asymptomatic response [26] .Increasing evidence suggest the possibility of the severity of the disease correlating with genetic variations in victims and not the genetic nature of the virus [27]. There is no path gnomonic feature of EVD. However, evidence indicates that some of the clinical features are indicative of the severity of the disease [28].

Gastrointestinal symptoms of anorexia, abdominal pain and diarrhea and difficulty in breathing may be similarly seen in ebola survivors and non survivors [28].

Neurological symptoms: confusion, loss of consciousness or coma were more frequent in those that died than the survivors [28]. Hemorrhagic symptoms: bleeding from puncture sites like needle sites, vaginal bleeding in females, haematemesis, epistaxis, bleeding from gums manifested more in the fatal cases [28]. These perhaps are secondary to disseminated intravascular coagulopathy. Miscellaneous symptoms of chest pain, cough and sore throat were seen more in those who died from the disease [28].

An Appraisal of the Outbreaks:

With reference to the table above, Ebola has recently directly or indirectly transmitted in three continents. Equatorial African region has experienced ebola outbreaks since 1976 almost four decades, some of the countries with repeated outbreaks. Despite their weak healthcare system, they appeared more readily prepared with high index of suspicion which favors their early detection of cases. There are readily available laboratory services for rapid and reliable diagnosis, isolation wards, trained staff on ebola infection prevention and control [29].

Governments treat confirmed ebola as a national emergency in this sub region [29]. On the contrary, risk factors in the recent West Africa sub region outbreak which so far was the deadliest of the outbreaks since its onset in 1976, was fuelled by inexperience and lack of preparedness for the outbreak. The borders are porous and high population mobility making spread easy and across border contact tracing difficult [29]. Very ill sneak across border easily to

safer countries for care exporting the virus. Cultural practices and behavioral practices such as traditional ancestral burial and funeral practices were linked to 60-80 cases in Guinea and Sierra Leone [29].

There was high reliance on traditional healers and herbalists which delayed early effective intervention with consequent increased transmission and mortality. Spread by international air travel play a vital role in the importation of the virus to Lagos Nigeria, Dallas Texas USA, and Europe. This was the marking of importation of Ebola across the borders via air travel [29].

Twenty first century brings with it increased and rapid cross-border mobility due to high global interconnectivity and interdependence therefore an ebola transmission any point on the globe puts other points, in fact the entire globe at the risk of importation by storm the invisible deadly cargo, ebola virus.

The two imported cases in Spain died while the female health attendant to one of them who contracted the virus was successfully managed. Similarly a medical evacuee the only confirmed case in 2014 outbreak in UK was successfully managed. There were few other imported cases in Europe mostly in Germany and Netherland. The lesson here is that ebola has lost its barriers and confines therefore an outbreak anywhere anytime should be treated as a global public health emergency before it breezes into our bed rooms since man can traverse round the globe just an airplane travel. Currently as at January 2015, 8641 deaths have been reported in six most affected countries; Liberia, Guinea, Sierra Leone, Nigeria, USA and Mali and 21,689 reported cases were even considered by WHO as being under reported. UN health agency declared an international public health emergency in West Africa outbreak. The coordinated teams of international agencies are still tirelessly battling Ebola to containment especially in sub-Sahara Africa.

It is pertinent to note the three categories of Ebola cases managed in the other continents outside Africa within the reviewed period. They were those infected and evacuated from West Africa epidemics, those diagnosed in USA and Europe after return from West Africa and three in all who contracted the disease from taking part in the management of the other two groups in their various countries.

Table: Ebola Outbreaks at a Glance as at 2014:

	Date	Country	Suspected focal of transmission	Number region affected	Number confirmed cases	Deaths	Case Fatality ratio
Central (equatorial) Africa: epicenter	1976,August	(Yambuku) Zaire(DRC)*	44 year old teacher	-	318	280	88.1
	1995,April	(Kikwit) DRC	-	-	316	250	79.1
	1976	Sudan	-	4	284	151	53.2
	2014	DRC	Unrelated West Africa outbreak	-	70	43	61.4
West Africa Outbreak	2014,March	Guinea**	18-month old boy	4	86	59	68.6
	2014,August	Guinea	-	2 new	1,825	1,096	60.1
	2014,March	Liberia	Across border from Guinea	All 15 districts	6,776	2,823	41.7
	2014,May	Serra Leone	,,	All	4,964	1479	29.8
	2014,July	Nigeria	Airplane traveler from Liberia	2	19	7	36.8
	2014,August	Senegal	Traveler from Guinea	1	1	0	-
	2014,October	Mali	Girl age 2yrs traveler from Guinea		8	6	75.0
Other Continents							
North America	2014,October	USA	Airplane from W. Africa	2	10	2	20.0
Europe	2014,	U K	,,	8 countries	14	5	35.7

*epicenter of the outbreaks. **Meliadou, Gueckedou Guinea origin of outbreak via a 2 year old toddler

Diagnosis:

Traditionally EVD or Ebola hemorrhagic fever (EHF) diagnosis relies on the viral isolation [30] and serological assay and antibodies detection [31] and Immunohistochemistry testing [32]. Due to High biosafety hazards only few recognized specialized laboratories perform the assays. High index of clinical suspicion is very important in this disease without path gnomic symptom. Diagnosis must be confirmed by detection of viral antigens or Ribonucleic acid (RNA) in the blood or other body fluids [16].

Treatment:

Currently there is no licensed vaccine for prevention or drug for treatment of ebola disease. These are still at various experimental levels of development. However some interventions have been applied with some promises especially if timely instituted. Confirmed cases should be

admitted in isolation ward best in designated center/treatment facilities. Early aggressive supportive care including rehydration and correction of electrolytes imbalance should be done. Life-saving supportive care is essential. Use of human interferon and convalescent serum has been previously tried [33]. The Core interventions including contact tracing, preventive initiatives, active surveillance, effective isolation and quarantine procedures and timely response to patients are essential for a successful outbreak control. [34]. These measures, combined with public health education, point-of-care diagnosis, promising new vaccine and pharmaceutical efforts and coordinated efforts of the international community, give new hope to the Global effort to eliminate Ebola as a public health threat [34].

Prevention and Control:

The key to management of EVD is its prevention and control. As at October 2014, there has not been any licensed vaccine for clinical use [35-37]. At personal level avoid areas of outbreak, wash your hands regularly, avoid contact with infected people or contaminated objects. Surveillance of border traffic to contain the disease in affected areas, setting up community ebola surveillance teams and closing of borders should be promptly effected at onset of outbreak. The identified contacts should be quarantined and physically monitored daily for 21 days for development of symptoms.

Health boarding, all departing and arriving travelers should be screened at the entry point at sea and air ports and frontiers to prevent importing and exporting the ebola virus among regions.

Government policies; banning crowding events like games and sports during outbreak, closure of schools, prompt and safe disposal of deaths should be ensured. Any identified ebola case should be seen and treated immediately as a national emergency by the government. All suspected cases should be managed in designated isolation wards and common treatment centers for confirmed cases. Good laboratory services especially good virology laboratory services are key to prompt diagnosis of cases. Point-of-care diagnosis should be the target. As a biosafety hazard the health personnel should be trained in handling the specimens and other materials which is crucial to contain the transmission. There should be quality protection of health workers who must be trained on the use of personal protective equipment (PPE) and application of barrier nursing procedures. Sanitation and personal hygiene are vital in the containment of Ebola outbreak.

National preparedness; regular revision and refining of the steps are vital.

Government should demonstrate strong leadership role by adequate and timely fund disbursement and coordination of all the activities via her health ministry. Prompt high quality contact tracing and movement of detected cases

to isolation wards to break transmission. Construction of isolation centers and designated treatment facilities; Prompt involvement of international agencies for early collaboration is essential for ebola containment.

Mobilization of all the relevant sectors for inter-sectorial collaboration as all have role in the case. Communication plays a vital role in social mobilization and ensuring early community involvement and support of containment measures. Health education; the print, electronic and social media public awareness campaign should be provided.

Door-to-door provision of information on preventive measures particularly sanitation, personal hygiene and the need for prompt reporting of symptoms and its prospects for survival should be carried out by the health personnel in local languages. The community, traditional and religious leaders should be used for sensitizing the public. In DRC outbreak of 1995, the outbreak was terminated by the initiation of barrier-nursing techniques, health education efforts, and rapid identification of cases [38]

CONCLUSION:

Deadly Ebola disease fast becoming endemic with its reemergence in some parts of sub-Sahara Africa is a great global health threat challenging the medical world especially in the recent wide rapidly spreading and ravaging outbreak in West African Sub region. Quality preventive and control measures, prompt contact tracing, safe and active management of cases backed by quality public education are crucial to its containment. Meanwhile the scientific world continues in search to unravel its mystery.

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