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THE STRENGTHS, WEAKNESSES, OPPORTUNITIES, AND THREATS (SWOTs) ANALYSES OF THE EBOLA VIRUS – PAPER RETRACTED

Michael Oluyemi Babalola

<sup>1</sup>Epidemiology, Molecular Virology, and Special Pathogens Research, Department of Microbiology, Adekunle Ajasin University, P.M.B. 001, Akungba Akoko, Ondo state, Nigeria.

Corresponding Author: Michael Oluyemi Babalola

Emails: [mikeolubabs@gmail.com](mailto:mikeolubabs@gmail.com), [michael.babalola@aau.edu.ng](mailto:michael.babalola@aau.edu.ng)

## Abstract

**Background:** Owing to the extreme virulence and case fatality rate of ebola virus disease (EVD), there had been so much furore, panic and public health emergency about the possible pandemic from the recent West African outbreak of the disease, with attendant handfull research, both in the past and most recently. The magnitude of the epidemic of ebola virus disease has prompted global interest and urgency in the discovery of measures to mitigate the impact of the disease. Researchers in the academia and the industry were pressured to only focus on the development of effective and safe ebola virus vaccines, without consideration of the other aspects to this virus, which may influence the success or otherwise of a potential vaccine. The objective of this review was to adopt the SWOT concept to elucidate the biological Strengths, Weaknesses, Opportunities, and Threats to Ebola virus as a pathogen, with a view to understanding and devising holistic strategies at combating and overcoming the scourge of EVD.

**Method:** This systematic review and narrative synthesis utilized Medline, PubMed, Google and other databases to select about 150 publications on ebola and ebola virus disease using text word searches to generate the specific terms. Relevant publications were reviewed and compared, findings were synthesized using a narrative method and summarized qualitatively.

**Results:** Some of the identified strengths of ebola virus include: Ebola virus is an RNA virus with inherent capability to mutate, reassort and recombine to generate mutant or reassortant virulent strains; Ebola virus has a broad cellular tropism; Natural Reservoir of ebola virus is unconfirmed but fruit bats, arthropods, and plants are hypothesized; Ebola virus primarily targets and selectively destroys the immune system; Ebola viruses possess accessory proteins that inhibits the host' immune responses; Secreted glycoprotein (sGP), a truncated soluble protein that triggers immune activation and increased vascular permeability is uniquely associated with Ebola virus only; Ability to effectively cross the species barrier and establish productive infection in humans, non human primates, and other mammals; Ebola virus attacks every part of the human body; The Weaknesses include: Ebola virus transmission and persistence is severely limited by its virulence; Ebola virus essentially requires host encoded protein Niemann–Pick C1 (NPC1) for host' s cell' entry; Ebola virus essentially requires host encoded proteins (TIM-1) for cell' entry; Relative abundance of Ebolavirus Nucleoprotein than the other virion components; The Opportunities harnessed by ebola virus include: Lack of infection control practices in African health-care facilities and paucity of health infrastructures, especially in the endemic zones; Permissiveness of circulating Monocytes, Macrophages and dendritic cells in virus mobilization and dissemination; Collection, consumption and trade of wild games (bushmeats); Perturbation and drastic changes in forest ecosystems present opportunities for Ebola virus; Use of dogs in hunting predisposes man and animals to inter-species contact; Poverty, malnutrition, crowding, social disorder, mobility and political instability; Ease of travel and aviation as potentials for global spread; Possible mechanical transmission by arthropod vectors; No vaccines or therapeutics are yet approved for human treatment; The Threats to ebola virus include: Avoidance of direct contact with infected blood and other bodily fluids of infected patient; Appropriate and correct burial practices; Adoption of barrier Nursing; Improved surveillance to prevent potential spread of epidemic; Making Available Rapid laboratory equipment and procedures for prompt detection (ELISA, Western Blot, PCR); Sterilization or disinfection of equipment and safe disposal of instrument; Prompt hospitalization, isolation and quarantine of infected individual; Active contact tracing and monitoring, among others.

**Conclusion:** The identified capacities and gaps presented in this study are inexhaustive framework to combat the ebola virus. To undermine and overcome the virus, focus should be aimed at strategically decreasing the identified strengths and opportunities, while increasing on the weaknesses of, and threats to the virus.

**Keywords:** SWOT of Ebola virus, EVD, Bats, bush meats, Niemann-Pick, DIC, haemorrhage.

## Introduction

Ebola virus is the etiological agent of Ebola virus disease (EVD), an acutely fatal haemorrhagic disease, that is characterized by high fever, body aches, joint pains, vomiting, diarrhea, multiorgan liquefaction, delirium, coma and death within two weeks of infection. Ebola virus has not been as successful in penetrating the human species because of its virulence and ferocity in devouring the host. “While HIV/AIDS is a silent stalker, Ebola is a violent, hot, and bloody predator”.

In accordance with one of the accepted methods of naming newly discovered viruses, Ebola Virus (EBOV) is named after a river in Yambuku area in the Democratic Republic of Congo (formerly Zaire) where the first outbreak occurred in 1976. There was a simultaneous outbreak in Sudan the same year. Literature has it that the index case was Mabalo Lokela, a 44 year-old male teacher at the Yambuku catholic mission school who fell ill after extensive travels in the northern Equateur Province of Zaire (now

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the Democratic Republic of Congo, DRC), having bought pieces of bushmeat (fresh and smoked antelope and monkey) as delicacies on his way back from the journey. At Yambuku, he took ill, and was treated for presumptive malaria at the Yambuku hospital. However, a week later, he had uncontrolled vomiting, bloody diarrhea, bleeding from the nostrils, mouth, and rectum, and died on 8<sup>th</sup> September 1976, about 14 days after the onset of symptoms. An outbreak of the disease ensued thereafter. Among the 318 human cases, 280 deaths (88% mortality) occurred, 38 serologically confirmed survivors were recorded, and the etiologic agent was identified to be Ebola virus, later renamed strain Mayinga, the prototype virus, after a Nurse Mayinga N'seka who died in the DRC outbreak (WHO, 1978).

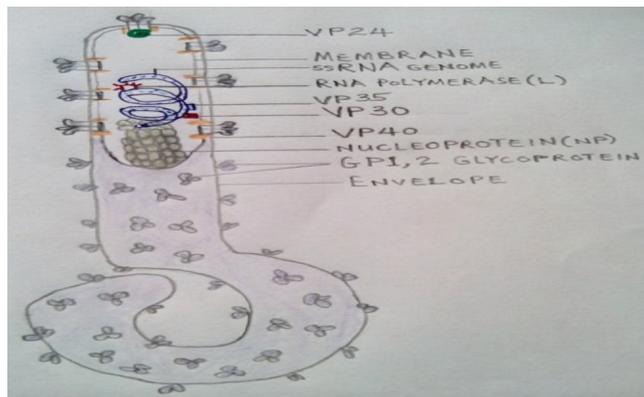
**Nomenclature of Ebola virus**

Ebola virus belongs to the Order Mononegavirales; Family Filoviridae; Genus *Ebolavirus*. By serology and genetic analyses, the distinct five virulent species are: *Zaire ebolavirus* ZEBOV (identified in Zaire in 1976, now renamed Ebola virus, EBOV), *Sudan ebolavirus* SEBOV (identified in Sudan in 1976, now renamed Sudan virus, SUDV), *Reston ebolavirus* REBOV (transmitted by *Macaca fascicularis* from Philippines, identified in 1989 in Reston USA, and in Sienna Italy in 1992, now renamed Reston virus, RESTV), *Cote d' Ivoire ebolavirus* CIEBOV (identified in Tai forest, CI in 1994, now renamed *Tai Forest ebolavirus*, TAFV), and *Bundibugyo ebolavirus* BEBOV (identified in Uganda in 2007, now renamed Bundibugyo virus, BDBV) (Kuhn et al., 2013).

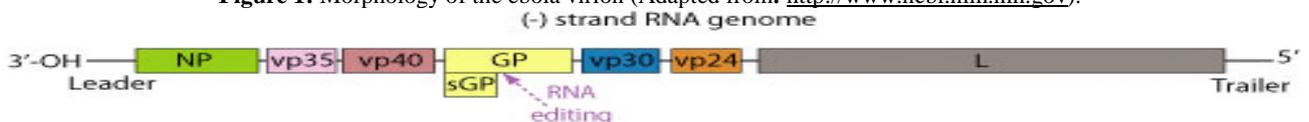
**Morphology of Ebola virus**

Morphologically, EBOV is a helical, enveloped RNA virus. Under the electron microscope, the virion is pleomorphic, long, sometimes branched, twisted, filamentous, thread-like, shaped like a “6”, “U”, a circle, or better still like a “hockey stick”. It is approximately 800-1400nm in length and 60-80 nm in diameter (Fig. 1). The genome (consisting of 7 genes) is typically approximately 19 kb (19,000 bp) in length of molecular weight 4.2x10<sup>6</sup> Dalton. The linear, non-segmented, negative-sense, single-stranded RNA is encoded in a 3' to 5' direction in an overlapping reading frame (Figs 1 and 2). The seven sequentially arranged genes are transcribed into 8 major mRNAs (7 structural proteins and 1 nonstructural protein). The proteins expressed by the ebola viruses are: nucleoprotein (NP) which encapsulates the RNA genome, glycoprotein (GP), RNA-dependent RNA polymerase (L), and four structural proteins, namely, minor matrix protein VP24, transcription activator (VP30), Polymerase cofactor (VP35), and VP40 (Fig 1). The Viral Matrix Protein VP40, and VP24 form the internal viral membranes while the surface of the viral envelope are spiked with arrays of glycoprotein GP trimers which are 10nm long and 10 nm apart (Feldmann et al., 1994).

Due to RNA editing, transcription of the GP gene results in the synthesis of several GP gene - specific mRNAs coding for viral glycoproteins including non-structural glycoprotein sGP and virion surface Transmembrane glycoprotein GP (Volchkov et al., 1998). Both glycoproteins are synthesized as a precursor molecule that is proteolytically cleaved by furin (a cellular protease) during intracellular processing (Volchkov et al., 1998). The sGP forms dimers (Falzarano et al., 2006) whereas the cleaved carboxy-terminal fragment, termed delta peptide, is a monomer (Volchkova et al., 1999). Viral envelope surface spikes are formed as a trimer of GP<sub>1,2</sub>, made up of two subunits, GP1 and GP2 linked by a disulfide bond (Jeffers et al., 2002). GP1 is known as the virus ligand which mediate virus attachment to the host cells' receptor whereas GP2 is involved in membrane fusion (Alazard –Dany et al., 2006). GP<sub>1,2</sub> is a type 1 glycoprotein containing multiple N- and O-linked glycans and the majority of O-glycans are grouped in a region termed mucin-like domain (Lee et al., 2008), while the GP trimers are the target for neutralizing and protective antibodies (Feldmann et al., 2001).



**Figure 1:** Morphology of the ebola virion (Adapted from: <http://www.ncbi.nlm.nih.gov>).



**Figure 2.** Schematic diagram and genomic arrangement of the Ebolavirus. Courtesy: <http://www.ncbi.nlm.nih.gov>

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EVD is a zoonotic disease, one that can be transmitted from animals to humans or from humans to animals. Majorly, Humans, bats, antelope, Deer, Pig, Chimpanzee, Gorilla, and Monkey are the culprits. In Africa, the major EVD outbreaks have occurred in these countries and years: the Democratic Republic of Congo (1976, 1977, 1995, 2007, 2008, 2012), Congo Brazzaville (2001, 2002, 2003) Sudan (1976, 1979, 2004), Cote d'Ivoire (1994), Gabon (1994, 1996, 1997, 2001), South Africa (1996), Uganda (2000, 2007, 2011, 2012), the 2013-2015 West Africa outbreaks in Guinea, Liberia, Sierra Leone, Mali, Nigeria, Spain, Senegal, USA, Spain, and UK (WHO, 2012; Carlos et al., 2014; Torpiano et al., 2014) resulting in a total reported case counts of 22,560 and confirmed mortality of 9,019 as at Jan 29 2015 (WHO, 2015). The epidemic is usually considered complete after an interval of at least twice the maximum incubation period (42 days) after the death or recovery of the last confirmed case. However, fresh cases were reported in Liberia and Sierra Leone in June 2015, month after the epidemic was declared over.

### **The Concept of SWOT**

SWOT is an acronym for Strengths, Weaknesses, Opportunities, and Threats. A SWOT analysis is usually represented as a grid. It is a business or strategic planning technique used to summarise the key components of the strategic environments. The technique is credited to Albert Humphrey at Stanford University between the 1960s and 70s, who led a research project that involved 5,000 interviews, funded by the fortune 500 and took 9 years to develop (Turner, 2002).

SWOT is a widely used framework for organizing and using data and information gained from situation analysis. The technique enables a group or individual to move from everyday problems or traditional strategies to a fresh perspective. It generally is a framework for identifying and analyzing the internal and external factors that can have an impact on the viability of a project, product, place, organism, or person. The SWOT concept was originally developed for business and industry, but it is equally useful in other areas, and even personal growth. SWOT is an assessment technique with a long track record of effectiveness. The strengths of this concept are its simplicity and application to a variety of levels of operation (Kotler, 1997). The benefits of SWOT include: identification of areas of strength and weakness, provision of comprehensive overview for contingency planning, and development of a "plan of action" to act on in a snapshot. SWOT analysis might be used to explore possibilities for new efforts or solutions to problems, to make decisions about the best path for an initiative, and is an excellent way to organize derived information from studies or surveys. The objectives of this innovative review was to educate all and sundry by adapting the SWOT concept to: identifying the biological strengths of ebola virus, determining the weaknesses of ebola virus, identifying the opportunities harnessed by ebola virus, determining the threats to ebola virus, present gaps where scientists and researchers could key-in for productive researches, and to encourage scientists, researchers, industry and the academia to explore this paradigm shift for holistic knowledge at combating recalcitrant, emerging, reemerging and potentially pandemic infectious pathogens and diseases.

### **Methods**

Databases used in this study included: Medline, PubMed, Embase, Web of Science, BIOSIS Previews and Google search engines. Text word searches (including "wildcards" to capture term variations, e.g., SWOT analysis, Ebola virus, Pathogenesis, diagnosis, zoonotic disease, Ebola virus disease, biological strengths of Ebola virus, weaknesses of Ebola virus, Opportunities harnessed by Ebola virus, Threats to Ebola virus, viral hemorrhagic fever, Disseminated Intravascular Coagulation) were conducted using keywords pertaining to Ebola (bats, monkeys, deers, bushmeat trade), bat-associated zoonoses and the urban environment (rural, endemicity, epidemicity, urban, city, cities, metropol). Groups of key words were combined using Boolean operators. Medline and Embase were searched using Medical Subject Headings (natural reservoir, fruit bats, zoonoses, Ebola virus disease, urban health, and human Ebola outbreaks) in various combinations. Papers in languages other than English and French were excluded. The literature search was conducted between August 2014, and March 2015. A total of 150 papers were identified for initial consideration. To ensure that the review was focused on the most up to-date researches, all papers published prior to 1976, and in languages other than English and French were excluded (n=12). Remaining papers (n=138) were organized for inclusion and reviewed according to the amount of information they contributed regarding the ecology, the strengths, weaknesses, opportunities and threats of Ebola virus pathogen associated with animals and humans. Papers with significant ecologic content (e.g., reviews, observational studies, modeling studies, large case series, studies focused exclusively on pathogenesis, pathogen genetics, treatment methodology, etc.) were retained (n= 140) and all other papers (e.g. case studies, short communications) were also included considering the importance of the virus (n= 10). Finally, papers not focused on the epicenter of ebola virus outbreak and monkeys/bats in urban centers (e.g., studies focused on other haemorrhagic fever viruses species, etc.) were excluded (n=15). Additional sources (n=5) were added through citation searching and to fill specific information gaps such as, biological strengths of Ebola virus. A total of 138 papers were reviewed in detail (Fig 3). Data from these papers were extracted and synthesized based on the methodology for narrative synthesis described by Arai et al. (2007). The goal of narrative synthesis is to identify common themes across research regarding a particular subject that then can be used to identify commonalities and critical differences among included papers.

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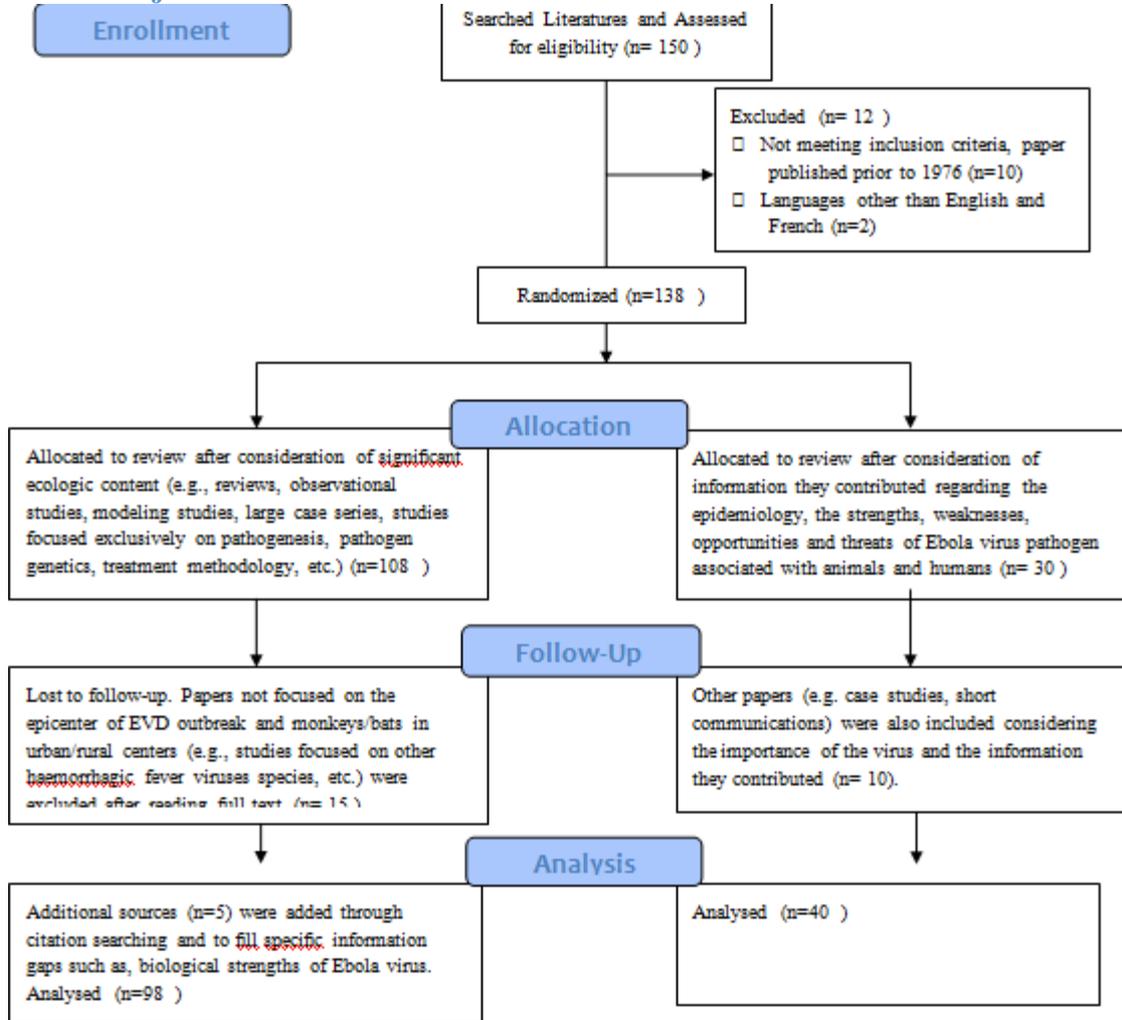


Figure 3: Flow diagram of Literature searches and the systematic review

## Results and Discussion

### STRENGTHS OF EBOLA VIRUS

Strengths are the characteristics of Ebola virus that gives it advantages over the host and other diseases. It comprises the positive tangible and intangible attributes, internal to Ebola. Essentially, the biological strengths and attributes that facilitate the pathogenicity, establishment, and spread of the Ebola virus include the followings:

**Ebola virus is an RNA virus with inherent capability to mutate, reassort and recombine to generate mutant or reassortant virulent strains.** Typical of RNA coded viruses, ebola virus mutates rapidly, both within a person during the progression of a disease and in the reservoir among the local human population, at a rate of  $2.0 \times 10^{-3}$  substitutions per site per year. This is likely to represent rapid adaptation to human hosts as the virus is repeatedly passed from human to human, and may pose serious challenges to the development of anti ebola vaccines (Biek et al., 2006). Bayesian phylogenetic analyses incorporating sequences derived from both human outbreaks and bats suggest that ‘spillover’ (Fig 4) occurs from bats to generate outbreaks in humans (Biek et al., 2006).

The 2012 outbreak of EVD in the Democratic Republic of Congo (DRC) was caused by the *Bundibugyo ebolavirus*. However, the cause of the 2014 Guinea outbreak has been confirmed by full-genome sequencing (Baize et al., 2014) to be an outlier strain (Gue’cke’dou-C05) of *Zaire ebolavirus*, the species from which the genus takes its name. Within species, divergence is rarely more than 4% (Gatherer, 2014). Recent study has shown that within EBOV, the species involved in the Guinea outbreak, the greatest divergence was 3% between the 1994 Gabon strain and the Guinea strain Gue’cke’dou-C05 (Baize et al., 2014).

The fact that the Guinea outbreak strain is an outlier within EBOV suggests that it is not an introduction of a central African strain into West Africa but has been present in bat populations in Guinea without previously infecting humans (Baize et al., 2014). Although it is yet to be proven if survivors of ebola virus disease possesses immunological memory to sustain immunity or to

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mop up subsequent reinfection, it is suffice to state that the susceptible host may not have developed immunity to fight the new mutant strains, with tendencies to elicit a pandemic.

**Ebola virus has a broad cellular tropism:** Cellular tropism is the affinity or propensity of a virus to preferentially establish interaction and attachment in a particular cell line when compared to the other cell types. While some viruses are only capable of interacting and replicating in a single cell line, others are efficient in replicating in multiple types of cell. The target cell range for EBOV infection is considerably broad. In-situ hybridisation and electron microscopic analyses of tissues from patients with fatal disease or from experimentally infected non-human primates show that monocytes, macrophages, dendritic cells, endothelial cells, fibroblasts, hepatocytes, adrenal cortical cells, and several types of epithelial cells were permissive of infection and lend support to replication of ebola viruses (Feldmann and Geisbert, 2011).

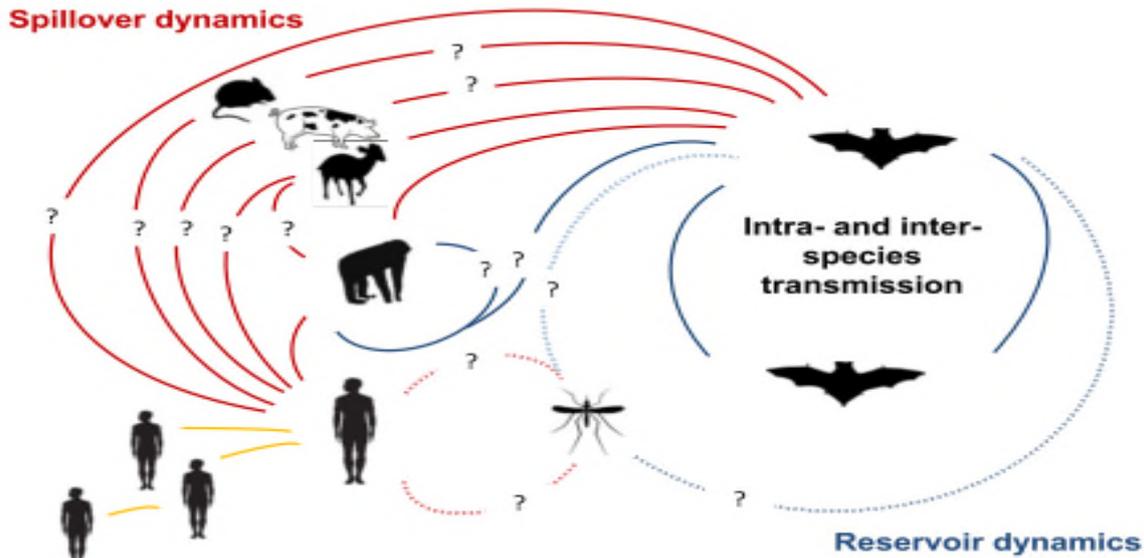


Figure 4. Ebola transmission Dynamics (Olival et al., 2014).

**Natural Reservoir of ebola virus is unconfirmed but fruit bats, arthropods, and plants are hypothesized:** The natural reservoir of a pathogen is the natural host that harbors the pathogen and in which it replicates without any clinical manifestation of the disease. The exact origin, locations, and natural habitat (known as the ‘natural reservoir’) of Ebola virus remain unknown. Very diverse taxa have been suggested as potential reservoirs for filoviruses over the years, including bats, rodents, arthropods, and plants (Germain, 1977; Arata and Johnson, 1977; Leirs et al., 1999; Swanepoel et al., 1996). The epidemiology and ecology of Ebola virus including identification of its natural reservoir hosts, remains a formidable challenge for public health and scientific communities. However, fruit bats of the Pteropodidae family are considered to be the natural host of the Ebola virus. Evidence of asymptomatic infection by Ebola virus was found in some species of fruit bat that are widely spread in Africa, including *Eidolon helvum*, *Hypsignathus monstrosus* (the hammer-headed fruit bat) *Myonycteris torquata* (the little-collared bat) and *Epomops franqueti* (Franquet’s epaulettes fruit bat) that migrate long distances (>2,500 km), indicating that these animals may be acting as a reservoir for the virus and could explain multiple remote epidemic clusters (Thomas et al., 1983). The first direct evidence from field studies that bats were reservoir hosts for Ebolavirus was reported by Leroy et al., 2005) and research has since been growing to understand the role that bats play in the maintenance, transmission, and evolution of filoviruses. It was hypothesized that lower animals such as palm civets pick up infectious ebola viruses from ejected remnants and saliva contaminated fruit pellets from fruit bats and culled indigestible insect parts by insectivorous bats. The discovery of EBOV sequences in fruit bats near the locations of human outbreaks implies that EVD is a zoonosis, transmitted from a reservoir in bats. Human Ebola outbreaks between 2001 and 2005 in Gabon and the DRC were linked to concurrent outbreaks that devastated local gorillas (*Gorilla gorilla*) and chimpanzee (*Pan troglodytes*) populations, making it unlikely that these non-human primates were the natural reservoirs but accidental or dead end hosts (Groseth et al., 2007).

**Ebola virus primarily targets and selectively destroys the immune system:** Ebola virus targets the immune cells by infecting and replicating in the dendritic cells, monocytes, macrophages, fibroblast reticular cells, and lymph nodes using the same method as HIV, to spread through the human body (Weingartl et al., 2013) before multiorgan involvement. Failure of early T-cell activation and extensive apoptosis of blood leukocytes lead to rapid systemic spread and death (Geisbert et al., 2003). Although EBOV does not replicate in lymphocytes, large numbers of these cells undergo apoptosis (Baize et al., 1999).

Recent studies indicate that Natural Killer (NK) cells, CD4+, and CD8+ lymphocytes are the principally infected target cells (Hotchkiss and Karl, 2003). Studies in macaques show that major features of illness are caused by effects of viral replication on macrophages and dendritic cells. Infected macrophages produce massive proinflammatory cytokines, chemokines and tissue factor, attracting additional target cells and inducing vasodilatation, disintegration of endothelial barrier, increased vascular permeability

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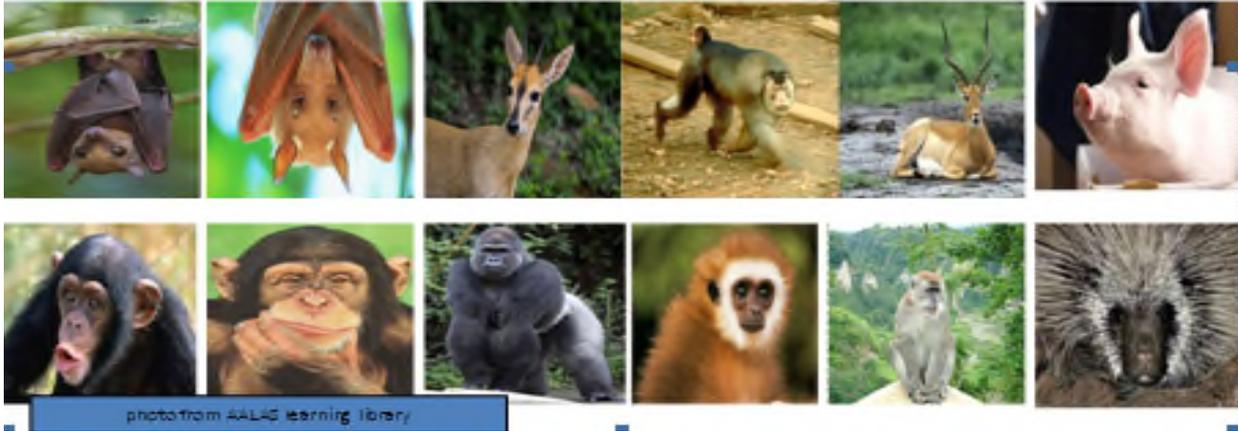
and disseminated intravascular coagulation. However, the macrophages cannot restrict viral replication, possibly because of suppression of interferon responses. Infected dendritic cells also secrete proinflammatory mediators, but cannot initiate antigen specific responses. In consequence, the virus disseminates to these and other cell types throughout the body, causing multifocal necrosis and a syndrome resembling refractory hypotension, Disseminated Intravascular Coagulopathy (DIC) and septic shock (Bray and Mahanty, 2003). The massive apoptosis of “bystander” NK and T cells further impairs the immune functions (Reed et al., 2004). However, in a study, treatment of infected macaques with a tissue-factor inhibitor reduced both inflammation and viral replication and improved survival (Bray and Geisbert, 2005). Therefore, these findings suggest that modifying host responses would be an effective therapeutic strategy against ebola.

**Ebola viruses possess accessory proteins that inhibit the host’ immune responses:** The VP35 protein is a Type I Interferon (IFN) antagonist that combats the host INF response. VP35 protein blocks IFN gene transcription and production by virus-infected cells. It prevents the cellular recognition of dsRNA that normally leads to phosphorylation of IRF-3 and its translocation to the nucleus. These activities are in concert with another viral protein VP24 which blocks responses to exogenous IFN (Basler and Palese, 2004). In effect, these inhibitory capacities impair antiviral defenses mediated by type I and II IFN needed to activate NK cells and upregulation of Major Histocompatibility Complex (MHC) for effective antimicrobial functions, thereby enhancing the replicative ability of the virus.

**Secreted glycoprotein (sGP), a truncated soluble protein that triggers immune activation and increased vascular permeability is uniquely associated with Ebola virus only:** Following infection, Ebola virus encoded glycoproteins (non-structural sGP) are uniquely released from infected cells in soluble forms into the host milieu. During EBOV infection significant amounts of both the virions and soluble glycoproteins, including shed GP and secreted sGP, are released from virus-infected cells into the extracellular environment. The soluble shed GP resembles virion GP 1,2, and has been shown to bind and sequester virus neutralizing antibodies directed against the surface GP (Dolnik et al., 2004). In addition, secretory glycoprotein (sGP) acts as decoys for immune cells and forms a dimeric protein that interferes with the signaling of neutrophils, which allows the virus to evade the immune system by inhibiting early steps of neutrophil activation. Contrary to other viruses’s glycoproteins, EBOV shed GP as a soluble mediator is able to activate non-infected immune cells, making it distinct from a number of other viruses whose surface glycoproteins have been shown to act as ligands for Toll-Like Receptor 4 (TLR4) recognition but that either do not shed their surface glycoproteins into the extracellular environment or do not spread systemically and thus only cause local inflammatory disorders (Xie et al., 2008; Bukreyev et al., 2008). The release of shed GP contributes to increased vascular permeability, DIC, disregulated inflammation and impairment of cell (hepatocytes and renal cells) functions and organ failure (Escudo-Perez et al., 2014) Therefore, as the shed GP has been found to possess a strong antibody-neutralizing role, it is conceivable that neutralizing antibodies targeting the shed GP could help to alleviate the systemic shock-like syndrome in EBOV infection.

**Ability to effectively cross the species barrier and establish productive infection in Humans, Non Human primates, and other mammals:** The species barriers separating nonhuman animal species from humans represent a major challenge for effective exposure to, infection by, and subsequent spread of zoonotic pathogens among humans (Kuiken et al., 2006). These species barriers can be divided into three largely complementary sets accordingly. First, the interspecies barrier which determines the nature and level of human exposure to zoonotic pathogens. Second, the intrahuman barrier which determines the ability of zoonotic pathogens to productively infect a human host and effectively cope with the immune response. Third, the interhuman barrier which determines the ability of zoonotic pathogens to efficiently transmit among humans, causing outbreaks, epidemics, or pandemics. Zoonotic pathogens may cross one or more of these sets of barriers, more or less efficiently. Only pathogens that cross the three barriers have the potential to sustainably establish in the human population (Gortazar et al, 2014). Identifying the factors that allow ebola virus to cross each of these three sets of barriers is essential to mitigate burdens of EVD. Notably, ebola virions are able to infect a broad range of primate cells, perhaps because the heavily glycosylated surface glycoprotein (GP) can bind to a variety of target molecules, including cell surface lectins (Takada et al., 2004). In addition, intensive domestic animal breeding facilitates viral mixing and increased targets for spillover from wild viruses (Taylor et al., 2001). Dogs and pigs are so far the only domestic animals identified that can be infected with Ebola Zaire. However, in Africa, infection has been documented through the handling of infected chimpanzees, gorillas, fruit bats, monkeys, forest antelope and porcupines found ill or dead in the forest.

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**Figure 5:** Potential hosts of ebola virus disease (Courtesy AALAS Learning Library).

**Multiple portals of virion entry:** Ebola virus enters the susceptible hosts through mucous membranes of the mouth, nose, eyes, skin cuts, abrasions, and open wound. Healthcare associated transmission occurs by reuse of needles and syringes, exposure to infectious tissues, excretions, and hospital wastes. Aerosol transmission has been proven in non human Primate but highly probable in humans.

**Transmission is enhanced by direct intimate person to person contact:** Through contacts with infected individuals, EVD debilitated, dead, or funeral apparels of dead individuals, the virus spreads to families and friends who come in close contact with infectious secretions when caring for infected persons.

**Ebola virus attacks every part of the human body:** Subsequent upon infection and replication, massive progeny viruses disseminate to every part of the body killing a huge amount of tissues, except the skeletal muscle and bones, converting it into a digested mass of virus particle. If the bones and skeletal muscles are spared during ebola infection, these sites could be researched and harnessed for generation of anti ebola medications.

**The virus can survive in liquid or dried material for a number of days:** Ebola virus is stable at room temperature or at 4°C for several days and indefinitely at -70°C. It is moderately thermolabile and can be inactivated by heating for 30-60 minutes at 60°C, and boiling for 5 minutes.

**Ebola virus is highly infectious at very low doses and has a short incubation period:** About 1-10 pfu of the virus is sufficient for infection. The time interval from infection with the virus to the onset of symptoms, is between 2 – 21 days, but more often within 4-9 days.

**Ebola induces severe hemorrhage and DIC on infection:** The bleeding phase typically begins within five to seven days after the first onset of symptoms. EVD patients expresses bleeding under the skin, the eye, and the orifices (nostrils, mouth, ears, genitals, rectum). The symptoms of hemorrhagic diathesis: bloody diarrhea, haematemesis, conjunctival injection, gingival bleeding, epistaxis and bleeding at the site of injection (Fig 6) are consistent with DIC, while skin manifestations include petechiae and puerperal (morbilliform skin rash) (Muyembe-Tamfum et al., 2012).



**Figure 6:** Haemorrhagic manifestations in Ebola patients: oral bleeding; skin, conjunctiva and diathesis at transfusion (Muyembe-Tamfum et al., 2012)..

**Ebola elicits complications and Induces multi-system collapse:** Ebolavirus damages many kinds of tissue in the body, either by direct infection of cells or by the body’s extreme inflammatory response. Cytokine release causes clots in the bloodstream, thereby

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blocking the blood flow to organs such as the liver and kidneys. Red blood cells are lysed when moving through small clot-filled vessels. As cells in the liver are destroyed, the blood loses its normal ability to clot, exacerbating any internal or external hemorrhaging. A breakdown of the adrenal glands leads to dangerously low blood pressure and a decreased ability to produce steroid hormones. The body's connective tissues are attacked and the extracellular matrices are broken down, as are the cells that line body cavities and surfaces, leading to accumulation of fluid in the brain. The resultant convulsions can cause patients to spew and spread infectious blood and bodily fluids. People who die from Ebola succumb to very low blood pressure, multiple organ failure, delirium, coma and the shock of severe infection (ECDC, 2014).

**Absence of carrier state and high mortality:** There is no carrier state. The case fatality rate (cfr) is between 60 – 90%. Previous outbreak had a cfr of 88% while the recent outbreaks were also above 50%. Ebola death (“crashing out”) ensues as early as 2 days after expression of symptoms and in many cases, death occurs between 7-16 days in 60-90% of cases, and recovery is usually painful (Muyembe-Tamfum et al., 2012).

**Confounding pattern of signs, symptoms and ill defined clinical course:** Variability of clinical presentations complicate early detection and management. EVD mimicks the presentation of other common diseases such as malaria, typhoid fever, and dysentery. Non-specific prodrome typically lasts less than 1 week. In ten to 12 days after the onset of disease, the sustained fever may break, with improvement and eventual recovery of the patient. However, between 1-2 weeks after onset of symptoms, hemorrhage and death occurs (Roddy et al., 2012).

**WEAKNESSES OF EBOLA VIRUS:** These are the characteristics that places the virus at a disadvantage relative to the host and the environment. The virus weaknesses detract it from its ability to attain the core goal, and influence its infectivity, growth, and establishment. Essentially, the internal attributes of Ebola virus that present as “Achilles’ heel” and targets for its elimination are:

**Ebola virus transmission and persistence is severely limited by its virulence:** Virulence is defined as the infectivity of a pathogen in a population and severity of the disease in the individual host. The basic model of virulence evolution is called the Trade-Off Model which states that disease virulence and transmission are negatively correlated. Higher virulence causes a disease to proliferate in a host, increasing host incapacitation and therefore potentially decreasing transmission potential. The high mortality associated with EVD represents an auto limitation for the virus expansion; this explains why most of the outbreaks began and ended in rural areas. It is infective only in the symptomatic stage and diffusion during the incubation stages is not reported by the literature. Ebola virus is ferociously pathogenic. It devours the patient rapidly, burns out the infected locality, thereby limiting its succession and sustenance during an outbreak. As long as contact with the case is cut off, transmission can be broken and the disease can be brought under control. This is where quarantine is important.

**Ebola virus essentially requires host encoded protein Niemann–Pick C1 (NPC1) for host’s cell entry:** A cholesterol transporter protein NPC1 is essential for Ebola virion entry and replication (Carette et al., 2012). The virus use the protein to gain entry into host cells, essentially tricking the cell into thinking that the virus is cholesterol. In a study, mice that were heterozygous for NPC1 were shown to be protected from lethal challenge with mouse-adapted Ebola virus. In another study, small molecules were shown to inhibit Ebola virus infection by preventing viral envelope glycoprotein (GP) from binding to NPC1 (Alexandra, 2011). Hence NPC1 was shown to be critical to entry of this virus, because it mediates infection by direct binding to the viral GP (Cote et al., 2012). When cells from Niemann Pick Type C patients lacking this transporter were exposed to Ebola virus in the laboratory, the cells survived and appeared impervious to the virus, further indicating that Ebola relies on NPC1 for cell entry. Therefore, mutations in the NPC1 gene in human were conjectured as a possible mode of effecting resistant in some individuals to this virus (Babin et al., 2014).

**Ebola virus essentially requires host encoded proteins (TIM-1) for cell’ entry:** T-Cell immunoglobulin and mucin domain1 (TIM-1, aka HAVCR1) was shown to bind to the receptor binding domain of the EBOV glycoprotein, to increase the receptivity of Vero cells in vitro. Silencing its effect with siRNA prevented infection of Vero cells. TIM-1 is expressed in tissues known to be seriously impacted by EBOV lysis (the trachea, cornea and conjunctiva). A monoclonal antibody against the IgGV domain of TIM-1, ARD5, blocked EBOV binding and infection. These studies suggests that TIM-1 may be potential therapeutic targets for an Ebola drug as a basis for a rapid field diagnostic assay (Kondratowicz et al., 2011).

**Relative abundance of Ebolavirus Nucleoprotein than the other virion components:** The filovirus Nucleoprotein consists of 739 or 695 amino acid residues, with a conserved hydrophobic N-terminus and a variable hydrophilic C-terminal (Niikura et al., 2001; Sanchez et al., 2007). The NP plays an important role in the replication of the viral genome, it is essential for formation of the nucleocapsid (Watanabe et al., 2006) and the C-terminal half has strong antigenicity (Saijo et al., 2001). The conformational and linear epitopes of nucleoprotein have been identified for several Ebola viruses (Ikegami et al., 2003) from which recombinants can be developed. Therefore the filovirus nucleoprotein may be an ideal target antigen because of its strong antigenicity and abundance in filovirus particles (Niikura et al., 2003; Bharat et al., 2012) for serological detection without handling live viruses.

**OPPORTUNITIES FOR EBOLA VIRUS:** These are the chances to make greater gains in the environment i.e external attractive factors that represent the reason for Ebola to exist, infect and spread. Opportunities arise when the virus can take benefit of conditions in its environment to infect and execute strategies that enables it to become established and spread. The various host and environmental factors harnessed for infection by Ebola virus are:

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**In an outbreak setting, the virus can be transmitted in several ways after the first case-patient:** EBOV disease is spread through infectious bodily fluids, including blood, excrement, saliva, breast milk, vaginal fluids, semen, and vomits by direct bodily contact with available viable infectious viruses in fomites, contaminated objects, reuse of needles or syringes and reinsertion into multi-dose vials of medicine. The virus can persist in semen for up to 61 days after the onset of illness and transmission through semen occurs up to seven weeks after clinical recovery (WHO, 2014) which could elicit infection and disease through sexual intercourse.

**Lack of infection control practices in African health-care facilities and paucity of health infrastructures, especially in the endemic zones:** Owing to the dearth of funding, medical equipment and accessories, patients are often cared for without the use of a mask, gown, or gloves, leading to exposure of health care providers (CDC, 2014) in the affected areas. In addition, disinfection of equipment are usually absent and slow to become available in numerous health facilities (Bah, 2014). As a measure, it is important to empower the local hospitals to shift reliance on distant facilities and also establish linkages /communication with International responders such as the CDC and the Medecins Sans Frontieres. African governments should establish effective and functional public health facilities with the appropriate infrastructure to cope with emergency situations and emergency preparedness. Social mobilization and awareness campaigns should also be strengthened to dispel dangerous rumors that encourage spread of dangerous infectious diseases.

**Permissiveness of circulating Monocytes, Macrophages and dendritic cells in virus mobilization and dissemination:** Ebola virus attacks immune cells. These cells seem to have pivotal roles in dissemination of the virus as it spreads from the initial infection site via monocytes, macrophages, and dendritic cells to regional lymph nodes, probably through the lymphatic system, and to the liver and spleen through the blood (Fig 7). Monocytes, macrophages, and dendritic cells infected with Ebola virus migrate out of the spleen and lymph nodes to other tissues, thus disseminating the virus to other tissues and organs in the course of the taxis (Schnittler and Feldmann, 1998).

**Diagnosis can be difficult as the symptoms can be confused with common diseases:** Early signs of ebola infection are non specific and mimicks malaria, dengue, lassa, and typhoid fevers. EVD is characterized by sudden onset of fever (>39°C), chills, malaise, exhaustion, sore throat, hiccups, rashes, headache, and joint/muscle aches. This is followed by diarrhea, vomiting, and stomach pains. Late signs are severe hemorrhage. The delay in clinical diagnosis and epidemic alert represent a major issue because it exacerbates the spread of the virus. Other variables that hinder the adequate management of outbreaks include training of health workers who fail to immediately identify the disease, especially in areas where EVD has never been observed, either because of nonspecific clinical symptoms or lack of experience (CDC, 2014).

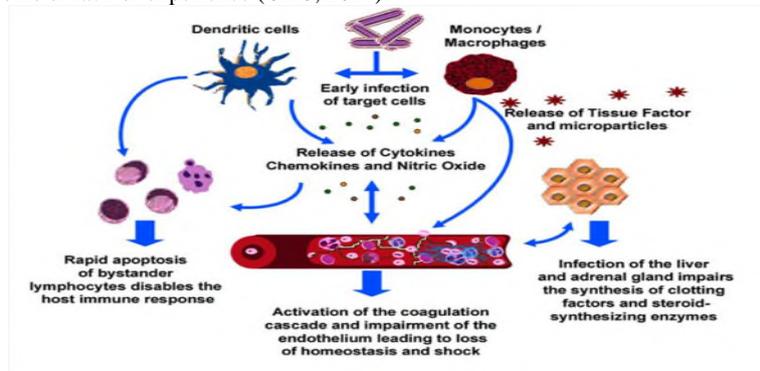


Figure 7: Pathogenesis of ebola virus disease (Hotchkiss and Karl, 2003).

**Collection, consumption and trade of wild games (bushmeat):** In areas where Non Human Primates were rare or absent, as in Kikwit (DRC) in 1995, Mweka (DRC) in 2007, Gulu (Uganda) in 2000 and Yambio (Sudan) in 2004, the hunting and eating of fruit bats were suggested to have resulted in the primary transmission of Ebola virus to humans. The index case of several outbreaks have been more or less directly associated with hunting or consumption of bush meat such as monkeys, antelopes, and bats (Leroy et al., 2009; Olson et al., 2012). About 13000 lbs of bushmeat were estimated to be imported into the UK annually. Therefore, the trade and consumption of ‘bushmeat’ should be highly regulated as these could serve as sources of outbreak in the respective destinations.

**Perturbation and drastic changes in forest ecosystems present opportunities for Ebola virus:** The reduction in biological diversity by deforestation can trigger the invasion and spread of opportunistic species, while the dry season attracts rodents to peridomestic environments, heralding the emergence of diseases through increased contact with local community. Human population in Africa has doubled in 27 years while native animal habitats have been destroyed or fragmented, and wild animal food sources made less diverse. When analysing the risk factors for primary transmission of EBOV from a broad anthropological point of view, it was noticeable that the increase in Ebola outbreak since 1994 was frequently associated with drastic changes in forest ecosystems in tropical Africa. The perturbation of these ecosystems due to extensive deforestation and human activities in the depth of the forests may have promoted direct or indirect contact between humans and a natural reservoir of the virus. EBOV infection has therefore

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been related to human economic activities like hunting (young hunters were infected by a chimpanzee in the forest near Mayibout, Gabon in 1996), farming (the infection of charcoal makers in the forest near Kikwit, DRC in 1995), and gold mining (in Minkebé Forest, Gabon in 1994). For instance, the forest region that borders Sierra Leone, Liberia, and Cote d'Ivoire was decimated by clear-cut logging, leaving the "Guinea Forest Region" largely deforested. Consequently, the region has found itself home to tens of thousands of refugees fleeing regional war and conflicts, adding to both the ecologic and economic burden. It is speculated that prolonged dry season, extreme deforestation, proportion of Ebola virus-infected bats and/or the frequency of human contact are some of the triggers of ebola virus outbreaks (Bausch and Schwarz, 2014).

**Use of dogs in hunting predisposes man and animals to inter-species contact:** Human settlements provide fertile grounds for interspecies transmission between wild /farm animals, rodents, dogs, cats, and insects. It is estimated that approximately 350,000 wild caught animals are traded around the world annually, adding to the risk of potentially zoonotic infections crossing the species barrier into humans. Once established in humans, the diseases could be maintained indefinitely. In 2009, a survey in Gabon found a greater than 30% seroprevalence for EBOV in dogs during the 2001–2002 outbreak (Barrette et al., 1989). An individual or animal who was likely infected from the suspected zoonotic reservoir on a hunting expedition in the forest would then cause secondary infections that may be amplified back in their local villages. Wild animals held or bred in captivity as companion animals, agricultural, research, or zoological parks, have long fascinated human societies. This implies that companion monkeys on long distance trucks, use of dogs for hunting as it is practiced in some African settings should therefore be discouraged. If domestic animals do indeed prove to play a role in the transmission through viral shedding of the Ebola strains to man, it may be necessary to develop veterinary vaccines.

**Poverty, Malnutrition, crowding, social disorder, mobility and political instability:** The effect of a stalled economy and government is 3-fold. First, poverty drives people to expand their range of activities to stay alive, plunging deeper into the forest to expand the geographic as well as species range of hunted game, to find wood to make charcoal, and deeper into mines to extract minerals, thereby increasing their risk of exposure to Ebola virus and other zoonotic pathogens in these remote areas. While the devastating effects of the civil wars in Liberia and Sierra Leone are evident and well documented, Guinea is in a state of stalled or even retrograde development. Guinea is ranked 178 (behind Liberia, 174 and Sierra Leone, 177) out of 187 countries on the UNDP Human Development Index. More than half of Guineans live below the national poverty line and about 20% live in extreme poverty. The indirect impact of the recent outbreak on the Guinean economy (and any other country affected) had been extensive, with the transport, tourism and entertainment sectors badly affected as people avoided crowded situations. Fewer workers have reported for work, thereby eventually having global implications, given that Guinea has one-half of the world's supply of bauxite, as well as significant iron, diamond and gold deposits (Bah et al., 2014b).

**Emotional and behavioral disposition of susceptible host by direct contact with the body or funeral apparels of deceased EVD patient:** Burial ceremonies in which mourners have direct contact with the body of the deceased can play a role in the transmission of Ebola. In the community setting, new infections related to the ministrations of funeral rites, which involve ritual cleansing of the cadaver and removal of hair, finger nails, toe nails and clothing before burial, constitute great risks. People visiting or taking care of infected persons in their homes or in hospitals also risk being exposed to Ebola infections (CDC, 2014). In the Guinean outbreak, the first death in the capital city of Conakry (population >2 million) was a businessman who had travelled from Dabola in central Guinea. He became ill on 17 March 2014 and died the following day. He was suspected to have contracted EVD in Dabola through contact with a visitor from Gue'cke'dou who also subsequently died from suspected EVD. The businessman's cadaver was taken from Conakry to Watagala, his home village (near Dinguiraye, north of Dabola). His four siblings who lived in Conakry, and who travelled with the body, and four other mourners at his funeral were all tested positive for EBOV (Guinea News, 2014). Thereafter, the total number of suspected cases presenting in the capital had risen (WHO, 2014b). Burial customs involving open viewing of the deceased potentially exposes the mourners to the virus and may amplify the spread of the virus. Learning to pay respect to the deceased person without touching or even seeing them would help reduce the spread of ebola.

**Demographics: changes in the age, race, gender, culture of residents in area of outbreak:** It has been shown, in several epidemics, that affected people perceived the illness as divine punishment or evil spell, and even, sometimes, denied the disease itself (Epelboin, 2012). Hesitations about diagnosis and the diversity of explanatory anthropological models result in the delay of the alert and difficulties in the implementation of measures against epidemics (Milleliri et al., 2004). Before appropriate measures are taken, which may take several weeks or months, the deceased persons are transported to their home community where people sometimes come from far away to attend the funeral and then go back home infected. The always frightening and often contradictory messages– and rumors– prompt patients to avoid going to the hospital due to fear of isolation and because of the lack of effective treatments. Even, violent protests– with loss of life, involving sometimes the medical staff– have been reported in some outbreaks. It becomes impossible to identify the cases, confirm diagnosis, protect and monitor contacts (Formenty et al., 2003). For instance it was beamed on GPBO Television and confirmed during the recent 2014 outbreak in Liberia, that some residents carried dead ebola victims on their heads, dead bodies littered the streets (Fig 9), violent protesters prevented health workers from intervening, with a consequential exponential increase in the number of cases after the protest (Adu unpublished correspondence).

**Inappropriate or even damaging evolution of effective defenses ("Cytokine storm") against the virus by the human and non human primate hosts:** The balance and timing of early immune responses to infection play a critical role in determining the outcome of infections (Bray and Mahanty, 2003). In the case of septic shock in EVD, fatal infection of humans appears to be associated with an elevation or overproduction of anti-ebola pro inflammatory cytokines. Survival appears to correlate with the

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development of an antigen-specific immune response, usually signified by the appearance of ZEBOV-specific IgG (Baize et al., 1999; Sanchez et al., 2004). If EBOV elicits damaging host responses, then therapeutic interventions that modify those responses may help the primate immune system to control viral replication and achieve survival.

**Ease of travel and aviation as potentials for global spread:** Frequent air travel is a major risk factor to the global spread of infectious diseases. It is estimated that over 100 million passenger- journeys by air are made annually. It is feasible to visit as many as three countries in a few hours. Road transport offers a more favorable route for transmission. Approximately 50% of all travel in Africa is by public road transport, compared to air travel which represents less than 0.2% of all passenger kilometers traveled. In contrast to airlines, public trains, buses, etc. are rarely fitted with high efficiency particulate air filters (HEPA). It is not only humans that travel: the International Air transport Association estimate that around 80,000 wild caught animals are air freighted each year, many being placed in holding facilities close to populated areas whilst in transit (Askar et al., 2012). The potential routes of transmission of infectious agents on board are mainly by inhalation of airborne droplets nuclei, direct contact with organic residues, indirect contact with respiratory secretions and other biological fluids contaminated surfaces. Spread of ebola cases over longer distances is often associated with ventures for treatment that draws people from rural villages that typify the index case locations to big urban centres with central medical facilities. While this mostly involves domestic land travel (Francesconi et al., 2003). some instances of international importation by air travel have been documented. The first travel-associated case of Ebola was reported on 30<sup>th</sup> September 2014 in the United States (USA), when an asymptomatic individual travelling from Liberia to Dallas, Texas developed clinical findings consistent with EVD and died five days after arrival in the USA and also infected two Nurses providing him healthcare (CDC, 2014). Following travel of an infectious individual, either secondary clusters of Ebola cases will occur, or transmission will be interrupted by control methods such as patient contacts tracing and quarantine (WHO, 2014c), as witnessed in the first index case in Nigeria (Fig.8). However, due to the highly incapacitating symptoms of Ebola virus infection, the probability that an affected individual undertake an air travel during the symptomatic phase is very low. Moreover the symptomatic passenger boarding should be prevented by control measures in place by the countries involved in the outbreak at the point of departure.



**Figure 8:** Spread of the 2013-2014 West African EVD outbreak (Torpiano and Pace, 2014).

Therefore, in response to public health emergency events of international concern, the airports located in areas of outbreaks must practice a screening of passengers from affected areas by visual inspection, questionnaires, and temperature measurement (thermal scanners and other available methods) rather than the screening made on arrival, to effectively limit the spread of the disease.

**Possible mechanical transmission by arthropod vectors:** The potentials of arthropods to act as mechanical vector is highly probable, particularly by houseflies that visited the dead (a scenario in the abandon of ebola dead on the streets of Liberia) during the overwhelming outbreak ( Fig 9).



**Figure 9:** An ebola dead victim lying in the street of Liberia during the 2014 epidemic (Source: Associated Press).

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**No vaccines or therapeutics are yet approved for human treatment:** The magnitude of the recent outbreaks of EVD and the likelihood of future human exposure and epidemic, underscores the necessity for pre- and postexposure therapeutics. However, none of the developed investigational drugs have been certified for human treatment. Therefore, absence of proven vaccines or drugs constitute opportunities for the virus to deride the host. It is hoped that as soon as an approved drug or vaccine is found the rage of the virus would be curtailed.

**THREATS TO EBOLA VIRUS:** Threats are external elements in the environment that could cause trouble for Ebola i.e. external factors, beyond an organization's (Ebola) control, which could place the virus' mission or operation at risk. Essentially, the external conditions that are inimical to Ebola virus establishment, and which may be harnessed for elimination of the virus include the followings:

**Avoidance of direct contact with infected blood, and other body fluids of infected patient:** At the very early stages when EVD is asymptomatic, ebola is not contagious but at the symptomatic stage, person-to-person contact should be minimized to interrupt transmission. In addition, direct contact with infected blood, urine, saliva, sweat, semen, breastmilk, vaginal fluids, mucus, phlegm, vomitus, and tears of infected patient should be avoided.

**Appropriate and correct burial practices:** Traditional practices regarding patient care and burial rituals often involve high risk conducts, such as washing and preparation of the body for exposure for several days, during which family and friends pay tribute by stroking or hugging the deceased (Hewlett and Amola, 2003). Decontamination can be presented as ablutions that can be associated with the burial rituals; deceased's clothes could be buried in the grave rather than burnt to prevent stigmatization etc, (Hewlett et al., 2005). Deceased people as a consequence of EVD must be handled using protective clothing and gloves, put into body bags and bury outside city immediately (Fig. 10). No washing or direct touching of the carcass of the dead should be made.



**Figure 10:** Proper handling and burial of ebola dead victims by health personnel.

**Adoption of barrier Nursing:** Nosocomial transmission through contaminated and poorly (or not) sterilized medical instruments is a major multiplication factor in most EVD outbreaks, particularly in remote and poor regions. Barrier precautions are used to prevent virus entry via the portals from blood, other body fluids, secretions (including respiratory droplets), or excretions. Barrier nursing procedures, such as protective clothing, hand gloves, face mask, mouth/nose guard, protective booths, shoe covers, proper waste disposals, use of Tyvek suits and respirators by Scientist and Healthcare Personnel are sufficient to rapidly interrupt transmission in hospital settings. Hand hygiene is strongly emphasized and should be performed thoroughly and often, including before and after donning and before and after doffing PPE. Patients isolation, use of the protective clothing and disinfection procedures are mandatory and sufficient to interrupt further transmission of Ebola virus, and thus to control and end outbreak (Raabea and Borcherta, 2012).

**Handling of all EBOV samples in BSL-4 facility, or minimum BSL-3:** Ebola virus is classified as Biological Level 4 (BSL-4) agents by Health and Safety Executive and as category A biological warfare agents (BWA) by the Centers for Disease Control and Prevention. Blood testing for definitive diagnosis and confirmation should be executed in National and International reference laboratories with BSL-4 facility. The nature of the virus make it suitable as BWA for the high lethality in human infection and for the potential oral and conjunctival transmissions via aerosolized virus suspensions in non-human primates.



Figure 11: A typical BSL-4 facility (Jean-Philippe, 2014).

**Future development and availability of pre- and post exposure prophylactics and therapeutics.** : Several vaccines are being developed but the two most advanced vaccines were based on recombinant vesicular stomatitis virus111 expressing an ebola virus protein VSV-EBOV (50% ZEBOV in Rhesus at 30 min) and the recombinant chimpanzee adenovirus expressing ebola virus protein (ChAd-EBOV). These were tested in humans for safety and efficacy in the United States of America and trials were started in Africa and Europe (Babin et al., 2014). The recombinant vesicular stomatitis virus111 vaccines have shown remarkable usefulness when given as a postexposure treatment against Ebola haemorrhagic fever in non-human primates. However, its use and efficacy in humans needs further studies. Others are FDA-Approved selective estrogen receptor modulators, SERMs (Clomiphene and toremifene) which inhibit EBOV. Recent studies have shown promise for a combination of monoclonal antibodies and for a small interfering RNA compound (BCX4430) as post exposure prophylaxis in non human primates (Warren et al., 2014). Key components of two of the most efficacious mAbs cocktails, titled MB-003 (MappBio) including antibodies c13C6, h13F6, and c6D8 and ZMAb (Defyrus) including antibodies c1H3, c2G4, and c4G7 have been recently combined and are in development for human use as a cocktail named ZMApp. The mAb components of ZMApp include c13C6, c2G4, and c4G7. Each of these antibodies was raised in vaccinated mice, chimerized into human IgG1 scaffolds and are mass produced in tobacco plants (Murin et al., 2014). Cocktail of Zmapp has already been used compassionately in a few patients with ebola. Use of plasma from patients who have recovered from infections, and drugs that affect coagulation such as recombinant nematode anticoagulant protein or recombinant human protein- C have also been tried and reported to be successful (Fieldmann and Geisbert, 2011). EBOV virulence also depends on its entry to immune cells via its surface glycoprotein, thus Compound 7, a benzodiazepine compound that binds directly to the EBOV entry glycoprotein, blocking infectivity has been developed, while Compound 8a also inhibited EBOV entry (Yemolina et al., 2011). These compounds displayed potent inhibition at low concentrations, but are yet to be evaluated for *in vivo* efficacy. Eventually, full development, trial, certification and acceptance of these investigational drugs in synergy with multivalent vaccines (properly engineered to overcome possible mutations of the virus that may render vaccination futile) against the 5 strains of ebola virus will constitute breakthroughs at enhancing the virus elimination.

**Managing patient' Hemorrhage by replacement of blood, platelets, and clotting factors:** Supportive treatment, maintaining oxygen and blood pressure level, fluid and electrolytes replacement, and treating any complications are some of the measures to mitigate ebola virus disease. Most often, palliative treatments are limited to rehydration with sugar solutions preferably orally to avoid injections, but sometimes not realistic because of throat pain, vomiting and intense fatigue. Analgesic, antipyretic, antiemetic, anti-diarrheal and sedatives or antipsychotic drugs are recommended to ease agitated and anxious patients.

**Improved surveillance to prevent potential spread of epidemic:** Syndromic surveillance should be instituted to identify groups of signs and symptoms that precede diagnosis by the use of Infra-red thermometers that can be simply operated.

**Making Available Rapid laboratory equipment and procedures for prompt detection (ELISA, Western Blot, PCR) :** A number of diagnostics and techniques are currently available for laboratory diagnosis of EVD. Acute infection is diagnosed by RT-PCR tests or ELISA to detect viral antigens. These tests can be positive from day 3 to day 15 of infection. Antigen can be detected in acute-phase blood by antigen-capture ELISA. The assay time is approximately 3 to 4 hours and the detection of antigen has been successful as compared to using PCR. Antibodies are tested either by direct IgG and IgM ELISA or IgM capture ELISA, IgM antibodies appear in blood by day 3 and disappear by 30 to 150 days. While IgG antibodies appear by day 6 and can remain in blood for many years. IgM or rising IgG titre constitutes a strong presumptive diagnosis (Sanchez et al., 2006). The virus can be isolated from acute-phase blood, liver, and other organs by inoculation into guinea pigs or cell culture (Strong et al., 2006). These technologies and personnel should be made available for use in the endemic areas.

**Miscellaneous measures:** Public awareness campaign, Strengthening health infrastructures especially in Africa where healthcare centres caring for people with the disease do not have tap water, Reporting to health authorities, Travel restrictions and system shut down may be instituted.

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**Sterilization or disinfection of equipment and safe disposal of instrument:** Appropriate concentration of calcium or sodium hypochlorite is effective to disinfect the premises, equipment, and other materials exposed to biological contamination from ebola patients (CDC, 2014b). Sodium hypochlorite is a lipid solvent, an inactivating agent which disrupts the viral envelope, the ligands, and in effect subsequent attachment and infectivity. Handy instruments, and fluids should be autoclaved. Sharps, used articles, beddings and linens should be incinerated. Patient’ excretions should be disposed off properly, and wash hands frequently using soap and water, or 70% ethanol.

**Prompt hospitalization, isolation and quarantine of infected individual:** Quarantine is regarded as enforced isolation of areas or individuals who may be infected. It may involve closure of schools, markets, worship congregations, or total shutdown of the system. These are milestones in reducing transmission of the virus. In the implementation of these threats, the ethical and social aspects should not be overlooked. Isolation of patients, required to avoid contamination, should not be seen as segregation. The family should be able to see and talk to patients, even if they are prevented from touching them. Authorities and medical staff should comply with, as far as possible, funeral rites by providing body bags and coffins for the families ( Boumandouki et al., 2005).

**Active contact tracing and monitoring:** Contact tracing involves finding everyone who had close contact with infected individuals and watching / monitoring for signs of illness for 21days. If any of the contacts comes down with the ailment, they should be isolated, tested, and treated. The process is then repeated by tracing the contacts’ contacts (CDC, 2014c) such as in the Nigerian index case experience. In respect of bus or air travel, as direct contact is the main route of transmission for Ebola, only the passengers who were seated in direct proximity to the index passenger should be included in the trace-back, i.e. only passengers who were one seat away from the index case (+/- 1 seat in all directions) should be traced back. If the index case occupied an aisle seat, the three passengers seated directly across the aisle from the index case should also be traced back (ECDC, 2010).

**Further research and treatment alternatives:** Considering the known / admitted challenges with vaccines, it is pertinent to consider addressing further research into exploiting, 1) the critical requirement (disulfide bond reduction / redox status) of viruses in cell entry. 2) A shift from the current paradigm in medicine which are heavily tilted toward the profitable Pharma model. We call for a worldwide integrative /alternative / holistic medical practitioners “in the field” for their experiences in treating otherwise difficult to treat infections, and a fair forum of reviewers (disconnected from the Pharma /profit or Pharma influenced universities and agencies) for their consideration. Such enlightened approaches could potentially successfully address other emerging recalcitrant infections which pharmaceutical based medicine fails to cure 3) Practitioners must evolve holistic support for the diseased body itself. From the clinical perspective, we need to explore how to augment the body in scaling up the activities of mediators such as the Reactive Oxygen Intermediates in combating pathogens, ozone therapy, replacement of Intravenous fluid electrolytes, lost macronutrients, optimizing trace minerals (required for normal immune function). 4) Optimization of other nutritional approaches (which might ultimately include IV Vitamin C, glutathione, etc for the ill, if simple ozone does not improve their status) as the African experience has shown that administration of Vitamin A mitigates complications of measles virus infection in children (Clement Adewunmi Personal Communication).

**Use of crematorium to dispose of carcasses:** Cremation is one of the best methods to dispose of the dead victims of EVD. However, this should be carried out with caution to avoid stigmatization of family of the deceased.



**Figure. 12:** Crematorium for Ebola casualties in the DRC

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	HELPFUL TO ACHIEVING THE PATHOGENIC OBJECTIVE	HARMFUL TO ACHIEVING THE PATHOGENIC OBJECTIVE
<b>Internal factors (attributes of the ebola virus)</b>	<p><b>STRENGTHS OF EBOLA VIRUS</b></p> <ul style="list-style-type: none"> <li>(i) Ebola virus is an RNA virus with inherent capability to mutate, reassort and recombine to generate mutant or reassortant virulent strains.</li> <li>(ii) Ebola virus has a broad cellular tropism.</li> <li>(iii) Natural reservoir of Ebola virus is unconfirmed but fruit bats, arthropods, and plants re hypothesized.</li> <li>(iv) Ebola virus primarily targets and selectively destroys the immune system.</li> <li>(v) Ebola viruses possess accessory proteins that inhibits the hosts' immune responses.</li> <li>(vi) Secreted glycoprotein (sGP), a truncated soluble protein that triggers immune activation and increased vascular permeability is uniquely associated with ebola virus only.</li> <li>(vii) Ability to effectively cross the species barrier and establish productive infection in humans, non human primates, and other mammals.</li> <li>(viii) Ebola virus attacks every parts of the human body.</li> <li>(ix) Multiple portals of virion entry.</li> <li>(x) Transmission is enhanced by direct intimate person to person contact.</li> <li>(xi) Ebola virus is highly infectious at very low doses and has a short incubation period.</li> <li>(xii) Ebola induces severe haemorrhage and DIC on infection.</li> <li>(xiii) Ebola elicits complications and induces multi-system collapse.</li> <li>(xiv) Absence of carrier state and high mortality.</li> <li>(xv) Confounding pattern of signs, symptoms and ill-defined clinical course</li> </ul>	<p><b>WEAKNESSES OF EBOLA VIRUS</b></p> <ul style="list-style-type: none"> <li>(i) Ebola virus transmission and persistence is severely limited by its virulence.</li> <li>(ii) Ebola virus essentially requires host encoded protein, Niemann-Pick C1 (NPC1) for host's cell' entry.</li> <li>(iii) Ebola virus essentially requires host encoded proteins (TIM-1) for cell' entry.</li> <li>(iv) Relative abundance of Ebola virus Nucleoprotein than the other virion components.</li> </ul>
<b>External factors</b>	<p><b>OPPORTUNITIES FOR EBOLA VIRUS</b></p> <ul style="list-style-type: none"> <li>(i) Lack of infection control practices in African health-care facilities and paucity of health infrastructures, especially in the endemic zones.</li> <li>(ii) Permissiveness of circulating Monocytes, Macrophages and dendritic cells in virus mobilization and dissemination.</li> <li>(iii) Collection, consumption and trade of wild games (bushmeat).</li> <li>(iv) Perturbation and drastic changes in forest ecosystems present opportunities for Ebola virus.</li> <li>(v) Use of dogs in hunting predisposes man and animals to inter-species contact.</li> <li>(vi) Poverty, malnutrition, crowding, social disorder, mobility and political instability.</li> <li>(vii) Ease of travel and aviation as potentials for global spread.</li> <li>(viii) Possible mechanical transmission by arthropods vectors.</li> <li>(ix) Emotional and behavioral disposition of susceptible host by direct contact with the body or funeral apparels of deceased EVD patient.</li> <li>(x) Demographics: Changes in the age, race, gender, culture of residents in areas of outbreaks.</li> <li>(xi) Inappropriate or damaging evolution of effective defenses (cytokine storm) against the virus by the human and non human primates hosts.</li> </ul>	<p><b>THREATS TO EBOLA VIRUS</b></p> <ul style="list-style-type: none"> <li>(i) Avoidance of direct contact with infected blood and other bodily fluids of infected persons.</li> <li>(ii) Improved surveillance to prevent potential spread of epidemic.</li> <li>(iii) Appropriate and correct burial practices.</li> <li>(iv) Adoption of barrier Nursing.</li> <li>(v) Making available rapid laboratory equipment and procedures for prompt detection (ELISA, Western Blot, PCR).</li> <li>(vi) Sterilization or disinfection of equipment and safe disposal of instrument.</li> <li>(vii) Active contact tracing and monitoring.</li> <li>(viii) Prompt hospitalization, isolation and quarantine of infected individual.</li> <li>(ix) Handling of all EBOV samples in BSL-4 facility, or minimum BSL-3.</li> <li>(x) Future development and availability of pre- and post exposure prophylactics and therapeutics.</li> <li>(xi) Use of crematorium to dispose of carcasses.</li> </ul>

**Table 1:** Contingency Table of SWOTs Analysis of Ebola virus.

## Conclusion

According to John F. Kennedy, "Change is the law of life and those who look only to the past or present are certain to miss the future." As a paradigm shift, the SWOTs concept can be adopted to help us as Scientists to formulate and apply strategies that augment our research and enable us to understand and combat emerging and/ or recalcitrant infectious diseases. Cumulative evidence from Africa has shown that the continent is developing and not economically buoyant, We think that a concurrent research into natural approaches alongside the synthetic medicines, for the possibility of discovering good treatment (like the wonderful wormwood, the source of artemisinin in malaria therapy) will be worthy of consideration. Adoption of the SWOTs concept is a promising research strategy to the discovery of leeway to mitigate the impact of Ebola virus. The identified capacities and gaps presented in this study are inexhaustive framework to combat the ebola virus. To undermine and overcome the virus, research focus should be aimed at strategically decreasing the identified Strengths and Opportunities, while Increasing on the Weaknesses of, and Threats to the virus (Table 1). Mankind are dealing with a major threat to human life on earth, and a transboundary disease that could easily be turned into a weapon.

It is pertinent to state that Ebola virus explores its biological strengths, conserves its weaknesses and exploits the host opportunities to decimate human population. Human induced environmental changes, inter-species contacts, altered social conditions, demography and medical technology affect microbes' opportunities. The academia and the industry should scale up all promising research findings and build more on the threats to the virus.

Although ebola is endemic in some African Nations, the recent epidemic experience shows that it has the capacity to garner pandemic proportion if adequate responses and controls are not effected. Therefore, all nations should proactively constitute Ebola Response and Control Committees as one of the proactive measures to curtail the disease. The development or strengthening of strategies and plans of action with timely and effective response in order to reduce the consequences of public health emergencies is imperative. By holistically harmonising all the identified factors, putting them into perspective and implementing our strategies, we can win the Nobel prize for overcoming the Ebola virus.

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