



Global Epidemiology of EBOLA Disease: A Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AS and CO designed and supervised the study, made corrections to manuscript and prepared final draft for submission. Authors AA, MB, KC, DJ, MJ, AM, PM, DS, MS and AS wrote the first draft of the manuscript, managed the literature searches and analyses of the study, author OB contributed to the professional content of the manuscript haven participated as part of the healthcare team from Nigeria for the control of Ebola in Liberia, and also made final corrections to manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

EVD is a disease of humans and other non-human primates caused by *Ebola viruses*, which was first discovered in 1976. Between 1976 and 2013 there had been 24 outbreaks of the disease. The recent outbreak is the 26th and has seen more deaths than all other outbreaks from the disease combined. This outbreak in West Africa occurred in five countries: Guinea, Liberia, Nigeria, Senegal and Sierra Leone. In the present research article, the authors reviewed various studies and current research on EVD. EVD was initially restricted to West Africa when the outbreak was first identified, but later was reported in several countries around the world, including the USA. Researchers have

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begun to use mathematical analysis from previous outbreaks to construct the Atangana's Beta Ebola System of Equations (ABESE), which is being used to predict the spread of future outbreaks. The pathophysiology and transmission factors, including the basic and effective reproduction numbers, R_0 and R_e are discussed in detail. Prevention and control measures, such as proper hygiene techniques (both preventative and post-exposure), education (including educating communities on proper burial techniques), reduction in the consumption and exposure to bushmeat, and controlled prevention of the spread of the disease (proper personal protective equipment and protocol upon exposure or in high-risk environments), are outlined. The history and current outbreak are reviewed in detail, which compare the differences in previous outbreaks compared to the current. Earlier (and less deadly) outbreaks have also been traced to the ZEBOV strain, and researchers suggest that the evolutionary rate of gene mutations was accelerated in this current outbreak. Death occurs in approximately 40% of affected individuals within 7-12 days after the onset of initial symptoms and is most often associated with multi-organ failure. Researchers outline the WHO's criteria for screening and diagnosis, including primary, secondary and entry screening. There is currently no cure for EDV, only supportive treatment. There are current drug trials on the following vaccinations: ZMapp, TKM-Ebola, Favipiravir, cAd3 and VSVA-EBOVGP12. This review article will attempt to summarize the current state of understanding on EVD and explore the most recent and accepted information including epidemiology of the disease, etiology and pathophysiology, transmission, prevention and control, history, recent outbreaks, clinical manifestations, screening and diagnosis, and treatment and clinical trials.

Keywords: Ebola virus disease; outbreak; surveillance; RNA virus.

1. INTRODUCTION

Ebola virus disease (EVD), also known as Ebola hemorrhagic fever (EHF), is a disease of humans and other primates caused by *Ebola viruses*. The disease was first identified in 1976 during two simultaneous outbreaks in sub-Saharan Africa, one in Nzara and the other in Yambuku, a village near the Ebola River, from which the disease takes its name [1]. The most widespread epidemic of EVD in history is currently ongoing in several West African countries. Between 1976 and 2013 there were 24 outbreaks, the most recent being the 26th. The 24th outbreak was first reported in Guinea in December 2013 and later spread to Liberia and Sierra Leone. As of March 12, 2015, the most recent outbreak has 24,350 reported cases resulting in 10,004 deaths [2].

Past outbreaks were brought under control within weeks, however this is the first EVD outbreak since its discovery to become an epidemic. The failure to control the epidemic may be due to its occurrence in areas of extreme poverty, dysfunctional healthcare system, distrust of government officials after years of armed conflict, and the delay in responding to the outbreak for several months [1].

Symptoms of the disease typically present within two days to three weeks of contracting the virus and include, but are not limited to fever, sore

throat, muscle pain, and headaches. As the disease progresses, vomiting, diarrhea, rash, decreased liver and kidney function, and internal or external bleeding may occur. The disease has a high risk of death, killing between 25 and 90 percent of those infected, with a recent average of 71% [1]. Infected patients usually die within six to sixteen days following onset of symptoms, most commonly due to low blood pressure from fluid loss [3].

The virus spreads by direct contact with body fluids of an infected human or animal. Even after recovery from EVD, semen or breast milk may still carry the virus for several weeks to months. The natural reservoir of EVD is unknown, but fruit bats are believed to be the likely reservoir and are able to spread the virus without being affected by it. Blood samples are tested for viral RNA, viral antibodies, or for the virus itself to confirm the diagnosis [4].

Control of outbreaks requires a myriad of tightly regulated precautions and procedures including coordinated medical services, alongside community involvement. The medical service surveillance includes rapid detection of cases of the disease, contact tracing of those who have come in contact with infected individuals, quick access to laboratory services, proper healthcare for those who are infected, and proper disposal of the dead through cremation or burial [4].

There is no specific Food and Drug Administration (FDA) approved treatments or vaccines for the virus, although a number of potential treatments are being studied. Supportive or palliative care, including oral rehydration therapy and intravenous fluids, can treat symptoms and improve outcomes of the disease. As the outbreak continues and cases continue to be reported in Guinea and Sierra Leone, the common goal is to gain control of the disease and eradicate it.

This review article will attempt to summarize the current state of understanding on EVD and explore the most recent and accepted information including epidemiology of the disease, etiology and pathophysiology, transmission, prevention and control, history, recent outbreaks, clinical manifestations, screening and diagnosis, treatment and clinical trials.

2. EBOLA EPIDEMIOLOGY

2.1 Surveillance and Bio-monitoring

The recent Ebola virus outbreak in West Africa occurred in five countries: Guinea, Liberia, Nigeria, Senegal and Sierra Leone. A total of 11,296 cases, including confirmed and probable cases were reported [5]. Although the Ebola virus outbreak was initially restricted to West Africa, in July of 2014, two American health care workers in West Africa were diagnosed with Ebola and then transported to a hospital in the United States of America (USA) for treatment. Later in the same year, a person who recently traveled to an Ebola-infected country was diagnosed with the virus in Texas [6].

Through proper surveillance, the USA, West African countries, and non-infected countries can: examine the effectiveness of current control and preventive health measures, keep track of changes of the infectious agent (Ebola virus), support health planning and designate appropriate resources within the healthcare system, identify high risk populations as well as areas needing targeted interventions, and also provide a record of disease activity for future reference [7].

The 2013-2014 EVD outbreaks mimicked the Ebola outbreak of Zaire in 1976. The causative organism of both was *Zaire Ebola virus* and they began in rural forest communities. Those infected with EVD reported to hospitals with

symptoms resembling those of malaria, typhoid, Lassa fever and/or influenza. Healthcare professionals were unprepared to handle the virus and some even came in contact with infected patient's bodily fluids, further exacerbating the outbreak. To stop the spread of the EVD in Zaire, the government quarantined the people, commercial planes and boats were not allowed in the country, and citizens were not permitted to leave their villages. The remains of the deceased were properly disposed of by cremation or placed in metal caskets according to the guidelines enforced by the Center for Disease Control and Prevention (CDC) for postmortem preparations. Surveillance teams led by trained healthcare professionals visited the 550 villages. Teams wore protective gear and brought first-aid kits, thermometers, antimalarials, antibiotics and antipyretics. Patients displaying symptoms of a fever were given medication and advised to stay isolated from others. The most recent Ebola virus outbreak was treated similarly to the outbreak of 1976. Priorities included the identification of infected patients and surveillance and care of those patients and their close contacts [8].

New York City (NYC) is a common entry point for travelers from West Africa; thus, safety precautions were implemented to prevent an outbreak of Ebola virus in the United States. This involved screening checkpoints set-up at various international airports around the world, including, but not limited to, the United States: Atlanta Hartsfield-Jackson International Airport, Newark Liberty International Airport, Washington-Dulles International Airport, Chicago-O'Hare International Airport, and New York JFK International Airport [8]. The NYC Department of Health and Mental Hygiene (DOHMH) worked closely with local hospitals and physicians, non-governmental organizations, community groups, and city, state and federal agencies to control the current situation and reduce the outbreak from spreading.

Clinicians were required to call DOHMH immediately after identifying any patient that met the CDC case definition for a person under investigation (PUI): a person who traveled to an Ebola-affected area within 21 days of onset of symptoms i.e. fever over 38.6°C (101.5°F), severe headache, muscle pain, vomiting, diarrhea, abdominal pain or unexplained bleeding. Also, obtaining a full travel history from febrile patients is needed to further avoid an Ebola outbreak. Although it is a challenge for

health care providers to remain vigilant for high-consequence diseases that occur rarely, it is of critical importance to be prepared for such a case [9].

To effectively estimate the spread of future Ebola outbreaks, mathematical analysis from previous outbreaks have been utilized to construct the Atangana's Beta Ebola System of Equations (ABESE). The equations were modeled after classical derivative and then modified to incorporate a time scale for the spread of Ebola via the beta derivative, which is a binomial coefficient between 0 and 1. Assuming that in a population of 1000 individuals with 900 being susceptible to Ebola, when beta is equal to 1, all individuals are infected and deceased, demonstrating an unrealistic outcome. The ABESE has shown to accurately estimate the amount of susceptible, infected, recovered, and deceased individuals for a given West African population when beta is less than 0.5. When looking at a period of time when rates of death, infection, recovery, and susceptibility of individuals have plateaued, the findings estimated 540 deaths, about 300 recoveries, 40 susceptible, and 10 infected [10].

2.2 Etiology and Pathophysiology

The pathophysiology or functional changes that accompany the single-stranded RNA Ebola virus is not fully understood; however, part of its pathogenesis has been elucidated [11]. Studies have suggested that the virus enters the host through mucosal surfaces, breaks and abrasions in the skin, or by parenteral introduction; though recent reports suggest that it is by direct contact with infected patients or cadavers. The organism has a broad cell tropism, which can infect a wide range of cell types. Studies in nonhuman primates have shown that fibroblasts, monocytes, dendritic cells, hepatocytes, macrophages, endothelial cells, adrenal cortical cells, as well as other cell types, have supportive features for the virus to replicate [12].

The Ebola genome codes for four virion structural proteins: VP30, VP35, nucleoprotein, and a polymerase protein. In addition, there is also VP40, glycoprotein and VP24 which is a three membrane associated protein within the virus. The surface glycoprotein is encoded in two frames: an open reading frame identified as OPF I and II. Open reading frame I encodes for a

small, soluble, nonstructural secretory glycoprotein (sGP) that is readily detected in the serum of the infected hosts [13]. This secretory glycoprotein binds to neutrophil CD16b, which is exclusively expressed by human neutrophils and binds IgG in immune complexes [11]. In other words, sGP is responsible for inhibiting early neutrophil activation and may also be responsible for the profound lymphopenia (a condition of having an abnormally low level of lymphocytes in the blood), a unique feature and characteristic of the Ebola infection [14]. Thus, studies suggest that sGP plays a pivotal role in the ability of the virus to prevent an early and effective host immune response.

In conjunction, there are other transmembrane glycoproteins, respectively referred to as GP1 and GP2 delta-peptide. These glycoproteins may also be incorporated into the Ebola virion. The exact mechanism is not fully understood; however, it is thought that these transmembrane glycoproteins are responsible for binding to endothelial cells of an unknown cell receptor but not to neutrophils. Therefore, the Ebola virus is known to invade, replicate in, and destroy endothelial cells [13]. Destruction of endothelial surfaces is associated with disseminated intravascular coagulation (DIC) and this may contribute to the hemorrhagic manifestations that are seen with late-stage Ebola infections. Clinical infection is associated with rapid and extensive viral replication in all tissues and accompanied by widespread and severe focal necrosis. The characterization of *filovirus* pathogenesis and a thorough understanding of the cellular mechanism are relevant to demonstrate the effectiveness of new biological products for control and prevention of the disease [15].

Fig. 1. The flow chart depicts the pathogenesis of *Ebola virus* infection. The mode of infection can be divided into three phases. Phase I is characterized as the transfer of the virus from an animal carrying the virus to a human, usually via small cutaneous lesions and subsequently, human-to-human transmission. Phase II is denoted as the early symptomatic stage. The early symptomatic stage typically occurs between days four and ten and is the stage of infection where symptoms of viral illness appear and progressively move toward more advanced manifestations of the disease. Phase III is representative of the advanced disease, with hemorrhagic manifestations, impaired immunity, and end-organ failure [11].

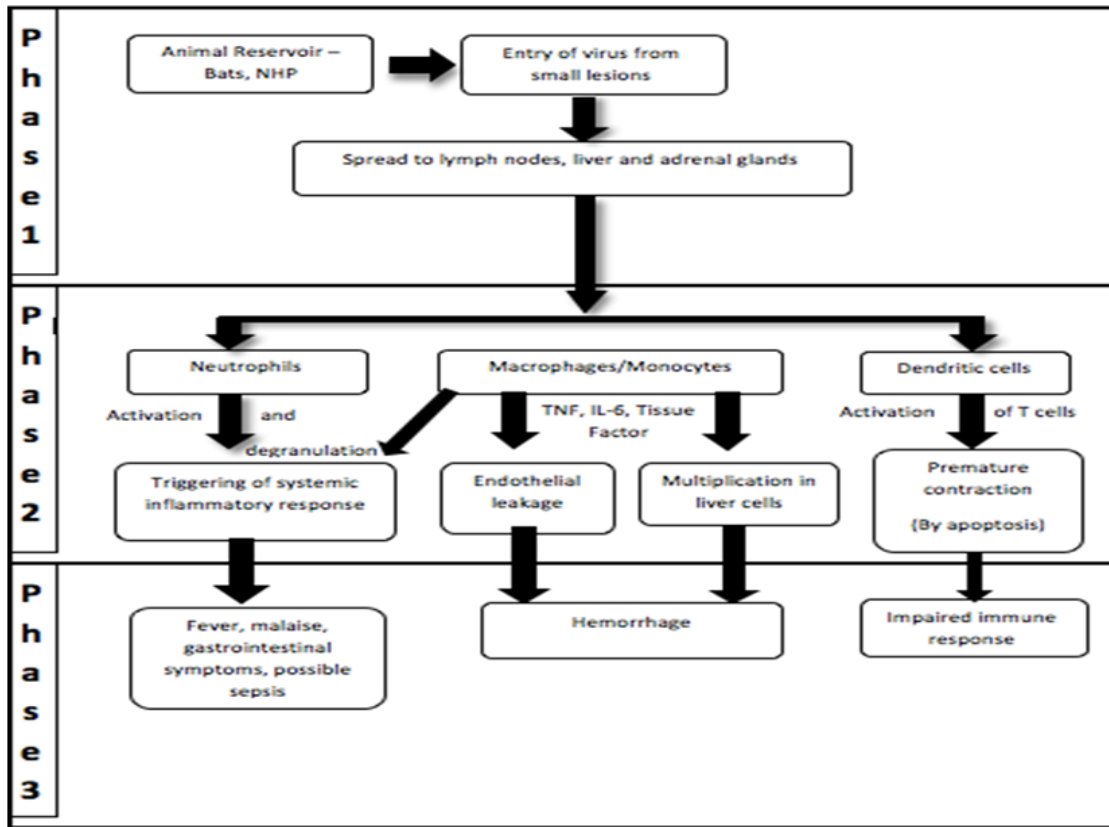


Fig. 1. The Pathogenesis of Ebola virus infection

Adapted from Kalra S. et al. (2014) [11]

3. TRANSMISSION

The causative agent of Ebola is an RNA virus of the family Filoviridae and genus *Ebola virus*. Five different strains of *Ebola virus* have been recognized, specifically *Zaire Ebola virus* (EBOV), *Tai Forest Ebola virus* (TAFV), *Sudan Ebola virus* (SUDV), *Reston Ebola virus* (RESTV), and *Bundibugyo Ebola virus* (BDBV) [16]. All strains are considered pathogenic to humans, except for RESTV [17]. However, the vast majority of past Ebola outbreaks in humans are associated with EBOV, BDBV and SUDV [18].

Human outbreaks are believed to result from direct human exposure to fruit bats or intermediate infected hosts, such as non-human primates or pigs [17]. The hammer-head fruit bat (*Hypsignathus monstrosus*) and the little collared bat (*Myonycteris torquata*) have been implicated as the most probable reservoirs for the virus [19]. Contact between bats and non-human primates may occur as they compete for

resources during the dry season. Once the initial zoonotic transmission has occurred, the human epidemic can progress by direct human-to-human contact. Sequencing studies conducted on 99 *Ebola virus* genomes from 78 patients in Sierra Leone suggest that while the initial transmission was zoonotic, subsequent transmissions are likely a result of human-to-human contact [20]. Human transmission occurs through contact with body fluids: Vomitus, diarrheal stool, blood, sweat, semen, saliva, breast milk, and tears [2,21]. Concerning the possible routes of transmission, transfer through saliva during the course of disease is particularly alarming because spread can occur through intimate contact and from food sharing, mainly because in Africa eating with hands from a common plate is customary [2]. Patients are considered infectious during the symptomatic period, and remain highly infective until they enter the recovery phase. Infected individuals are contagious when they begin to show symptoms and without isolation each Ebola patient is estimated to infect around 1-8 additional people,

leading to an exponential growth and a doubling time of 20 days [22]. Large outbreaks of *Ebola virus* are commonly spread by person-to-person transmission, with caregivers both at home and those in hospitals being at a higher risk [23]. Corpses are also viewed as highly infectious [21]. Unsafe burials that involve washing, touching and kissing Ebola-infected bodies are major infection risks [23,24]. Controlling transmission requires reducing contact with bodies, body fluids of infected person and contaminated items such as clinical wastes, clothing and mattresses [21]. Transmission does not occur through insect bites, airborne routes or water sources, so stopping transmission should be possible with early detection and proper management [4].

Information on the force of transmission of Ebola infection is critical to understanding and controlling the epidemic. Two important parameters used to describe the spread of an infection are the basic and effective reproduction numbers, R_0 and R_e [25]. The basic reproduction number, R_0 , is of particular concern when modeling an infectious disease as it provides a reference for dissemination within a population [26]. It is interpreted as the average number of secondary cases generated by an infected individual during the entire course of infection in a susceptible population and in the absence of control interventions [26]. Althaus described the EBOV epidemic using a SEIR (susceptible-exposed-infectious-recovered) model with time-dependency and fit the model to reported data of infected cases and death in Guinea, Sierra Leone and Liberia during the 2014 outbreak [25]. The estimates were 1.5 for Guinea, 2.5 for Sierra Leone and 1.6 for Liberia. In a population with a presence of control interventions or prior exposure, the R_e of a disease outbreak is quantified as the average number of individuals infected by each newly infected person. If $R_e < 1$, then an infected individual produces less than one newly infected individual, and the transmission may discontinue because it is not self-sustaining [26,27]. If $R_e > 1$, the only public health intervention that may be effective is a vaccination protocol; therefore, all other attempts will be overpowered by existing modes of infection. Public health scientists concluded that the R_e from June to August 2014 ranged between 1.4 and 1.7 in Sierra Leone and Liberia, and that efforts should focus on reducing R_e to below 1 [27]. The key to reducing R_e and controlling the epidemic is rapid diagnosis, isolation and treatment of infected patients.

According to estimates from the U.S. CDC, about 60% of all Ebola infection in West Africa was undiagnosed, and there is potential for marked increase in cases by mid-2015 [27].

4. PREVENTION AND CONTROL

Providing education to at risk populations is the key to preventing an Ebola outbreak. Through promotion of biosecurity (including infection-control education and proper supplies for hospitals), the risk of an outbreak will be reduced. Unfortunately, in many areas where Ebola outbreaks are common - such as the recent outbreak in Sierra Leone, prevention and control efforts, procedures, facilities, staffing, transportation of teams, and supplies were not sufficient to respond to such a dangerous epidemic [28]. While there are many elaborate, expensive, and advanced methods in regard to preventing the spread of the Ebola virus, proper hygiene is still considered one of the most useful preventive measures. Proper hand hygiene includes the use of alcohol-based hand rub or soap and running water. The uses of alcohol-based products, along with heat, and sodium hypochlorite (or calcium hypochlorite) have been shown to eliminate the Ebola virus from contaminated environments [29]. Utilization of soap and water or alcohol-based hand sanitizers have been proven to disrupt the envelope that contains virulent glycoproteins which coat the single-stranded RNA Ebola virus. Educating at risk populations about the importance and use of full personal protective equipment (PPE) and heavy rubber gloves, along with supplying these populations with these materials, is another preventative measure that is encouraged. Additional measures to reduce the number of outbreaks include providing guidance that encourages behavioral and cultural changes, such as safe burial methods and funeral ceremonies [23]. The remains of a deceased victim should be sealed in a double bag, wiped down with a 0.5% chlorine solution, and labeled as highly infectious material. The remains should then be placed inside a coffin and buried promptly. Post-mortem examination is not advised and should be limited to only essential examinations that are performed strictly by trained personnel [29]. The implementation of this is a difficult task due to long-standing local funeral practices that involve the touching of deceased persons, potentiating the spread of contaminated body fluids [23]. If an uninfected person comes into contact with body fluids containing the *Ebola virus*, the individual is

instructed to immediately and safely stop their current task, wash the exposed area with soap and water, irrigate mucous membranes with copious amounts of water and/or an appropriate solution, and report the incident to the local coordinator. The exposed person will then be evaluated medically and will receive follow-up care twice daily for 21 days post exposure [29]. This procedure also applies to those who had contact with the infected individual. Contact tracing, identification, and temperature monitoring daily for 21 days is required for each at risk or infected person. Another preventive measure is to reduce contact with bats as well as handling of bushmeat. This is difficult for some areas where bushmeat is the main sustenance for the local population; however, in these cases, safer slaughtering and handling are encouraged [23].

Once a person is suspected of contracting the Ebola virus, strict measures are set in place to control the risk of spreading the virus to unaffected medical workers and the local population. Suspected and confirmed patients are placed in single isolated rooms, or if not possible, in cohort areas where they are kept at a minimum of one meter distance apart. Access to affected patient rooms should be limited. Medical staff attending to infected or uninfected patients, as well as the patient visitors, should only be in the proximity of the infected patient if they are necessary for the patient's well-being and care [29].

Control measures are essential to prevent the spread of the disease to other patients, healthcare workers, and visitors [14]. Unfortunately, this basic control measure is hard to implement in certain regions of Africa because not only is the area stricken with a low ratio of health-care workers to population size, but it is also lacking in personal protective equipment, such as gloves, gowns and facemasks [14]. However, the World Health Organization (WHO) has established guidelines that all persons entering or exiting the rooms of infected patients (i.e. medical staffs, visitors, aides, cleaners, etc.) should follow. These guidelines include: 1) proper hand hygiene; 2) full set of personal protective equipment (PPE) including double gloves, gown, apron, mask, eye protection, and waterproof boots; 3) careful removal and disposal of PPE prior to exiting the room; 4) proper disposal of single use PPE and proper cleaning/decontamination of reusable equipment; and 5) dedicated equipment for each patient. The

cleaning technique applied varies depending on the type of reusable PPE, linens, and surfaces that the facility is using. Face shields and goggles should be rinsed with water to remove organic material, immersed fully in a 0.5% chlorine solution for a minimum of 10 minutes, and rinsed again with water. Before leaving an isolated area, boots should be decontaminated by stepping into a bowl of 0.5% chlorine solution for at least one minute. Boots should also be soaked in a bowl of 0.5% chlorine solution for at least 30 minutes once a day. Linen, which is heavily soiled, should be incinerated or processed by autoclaving; however, mildly soiled linen may be washed in a laundry machine with detergent and water, rinsed, and then soaked in 0.5% chlorine solution for 15 minutes. Hand washing the linens is highly discouraged. Tables and surfaces should be cleaned with a detergent containing 0.5% chloride solution, followed by the application of a disinfectant. Floors should not be swept, but rather wiped down with a moist cloth to prevent air contamination [29].

The WHO has also established procedures for waste management. Waste should be segregated at the point of generation and should not be stored for longer than 24 hours. Solid waste may be incinerated, autoclaved, or buried. When burying waste, a pit must have a depth of about 2 meters and filled to a depth of 1-1.5 meters. Waste, such as feces, urine, vomitus, and liquid waste from washing, may be disposed of in a sanitary sewer. This is due to the fact that the environment is capable of inactivating the Ebola virus faster than other enteric viruses [29].

5. HISTORY

The Ebola virus first appeared in 1976 during two outbreaks, which occurred simultaneously. The first occurrence was in Nzara, Sudan and the other was in Yambuku, the Democratic Republic of Congo. Later, the deadly virus occurred in a village in close proximity to the Ebola River, where the virus took its name. In the first outbreak, the virus infected over 284 people in Sudan, resulting in a mortality rate of 53% [1]. In Yambuku, Zaire, 318 people were infected with a mortality rate of 88% [1]. The next largest outbreak of the disease occurred again in the Democratic Republic of the Congo (formerly known as Zaire) in 1995. This affected 315 individuals with a mortality rate of 81% (250 casualties) [1]. This incident occurred in Kikwit and the surrounding area. It started through a case-patient who worked in the forest adjoining

the city and spread to the hospital [30]. Between 2000 and 2001, Uganda was struck by the Sudan strain of the virus; this strain infected 425 individuals with a mortality rate 54% (224 casualties) [31]. This viral strain occurred in Gulu, Mbarara, and Masindi districts of Uganda. Individuals who attended funerals of patients infected with the Ebola virus initially contracted the virus. Improper medical care to patients and lack of personal protective equipment for the medical staff contributed to the spread of the disease [32]. From December 2002 to April 2003, the Republic of Congo was affected once again by the Ebola virus, infecting 143 individuals and resulting in an 89% (128 casualties) mortality rate [32]. These outbreaks occurred in the districts of Mbomo and Mbandza villages. In 2007, four years later, the Republic of Congo was again affected with an increase in the number of cases. There were 264 individuals infected with the virus, resulting in a 71% mortality rate (187 casualties) [32]. Several years later, from March 2014 to present day, the number of reported cases in affected countries reached a total of 24,202 individuals that were infected with the Zaire virus. The mortality rate among these cases is 41% (9,936 casualties). This outbreak involved a number of countries across West Africa, including Guinea, Sierra Leone, and Liberia (Fig. 2) [31].

6. RECENT OUTBREAK SITUATION

The 2014 Ebola virus disease (EVD) epidemic was the largest and most complex, killing more people than all previous Ebola outbreaks combined [33]. Several West African countries were affected, primarily Guinea, Liberia, Sierra Leone with secondary cases in Mali, Nigeria, Senegal, Spain, and the United States [34]. As of August 12, 2015, there were 27,965 reported cases of Ebola virus infection, with a 40.4% mortality rate [35]. However, these statistics under reported the countless number of patients in developing countries that failed to seek local healthcare services. The obstinate progression of the outbreak can be attributed to deficient healthcare systems, mobile populations with uncontrolled borders, overcrowded cities, and funeral customs involving close contact with corpses [36,37].

The *Zaire Ebola virus* (ZEBOV) strain was associated with the 2014 Ebola outbreak in West Africa. Compared with earlier outbreaks involving the ZEBOV strain, researchers suggested that the evolutionary rate of gene mutations was accelerated in this current outbreak. This ultimately suggests that there were more ZEBOV variants that were being transmitted from human-to-human during this epidemic [33].



Fig. 2. The 2014 Ebola outbreak in West Africa - outbreak distribution map
Adapted from WHO, (2015) [1].

Researchers traced the 2014 Ebola outbreak to a 2-year old male from the small Guinean village of Meliandou who initially came down with symptoms of fever, vomiting, and black stools in December 2013. The initial source of transmission remains unclear. It was reported that a healthcare worker spread the disease to neighboring regions, and in the months following the index case, thousands of people living in Guinea, Liberia, & Sierra Leone died of similar symptoms [36]. In March 2014, the WHO declared a major Ebola outbreak in Guinea. After the initial report, the outbreak was considered to be self-limiting and restricted in geographic spread. Unfortunately, due to poor local health systems and people in the region traveling across rural areas along the border, the virus began to spread rapidly [38].

In August 2014, the United Nations Health Agency declared the Ebola outbreak an international public health emergency. A nurse aide in Spain was the first to contract the virus outside of West Africa when she cared for missionaries who had just returned from Liberia and Sierra Leone. On September 20, 2014, the first travel-associated case was reported in the United States and the patient eventually became the only lethal case in the US [36].

7. CLINICAL MANIFESTATIONS

The incubation period, i.e. the duration of time from infection to when the first symptoms of Ebola present, commonly occurs within a 4-10 day window (but may range from 2-21 days) [12]. Affected individuals generally presented to health care facilities on an average of 3.5 days from the onset of symptoms.

The most common early manifestations associated with Ebola infection include fever (84% of EBOV + individuals), fatigue (65% of EBOV + individuals), generalized weakness and body aches (77% of EBOV + individuals), and mild tachycardia [39,40]. Less commonly, individuals in the early stages of infection experience non-bloody watery diarrhea (>5 L/day), abdominal aches, and conjunctivitis [3]. Gastrointestinal symptoms, including nausea, vomiting, diarrhea, and abdominal pain, are seen in 81% of affected individuals and typically presents 3-5 days post onset of initial symptoms [39]. Headache, decrease in appetite, myalgia, and dysphagia tend to present 3.5-8 days post onset of initial symptoms [3]. Within 5-7 days post onset, patients may develop a nonpruritic

maculopapular rash that begins on the lateral part of the abdomen and spreads throughout the body (sparing the head), and oftentimes becomes difficult to observe in the African population [40]. Late onset symptoms that may occur include conjunctivitis and orchitis caused by the viral invasion of the anterior chamber of the eye and seminal fluid [41]. As the disease progresses, the patient may develop various forms of multisystemic pathologies as shown in Table 1. The total symptom load is predictive of disease progression and an increase in the number of symptoms is associated with a higher risk of mortality [3].

Death occurs in approximately 40% of affected individuals within 7-12 days after the onset of initial symptoms and is most often associated with multi-organ failure [40]. The three most indicative signs of lethality are the presence of hiccups, hemorrhage, and shock. Presence of hiccups (15-28% of EBOV + individuals), is often a fatal sign of unknown origin; preceding tachypnea which is almost always followed by death [39,41]. Hemorrhages located within mucosal tissues (gums, gastrointestinal, nasopharynx, and respiratory tract) and skin puncture sites occur at the peak of the illness. Hemorrhage is associated with increased prothrombin time (PT) and partial prothrombin time (PTT), failure of platelet function, and increased fibrin degradation products and is associated with hepatic and vascular damage. The patient may present with hematemesis, epistaxis, petechiae, hematuria, hematochezia, and melena. Melena is the only sign of bleeding that is not predictive of mortality [40]. Patients showing signs of hemorrhage have twelve times the risk of dying [3]. Approximately 50% of deceased Ebola individuals had signs of hemorrhage and 60% of patients developed shock due to hypovolemia, infection, and metabolic acidosis [12,31]. This typically leads to multi-organ failure and death [42].

The average duration of the disease is 9 day [3]. Ebola patients are discharged if PCR is negative for the virus and if they have gone 3+ days without gastrointestinal complications [40]. PCR may be negative for Ebola, but the virus may remain latent in tissues [43]. Approximately, 60% of these individuals survive. Ebola survivors in recovery may later die of arrhythmias or may develop a cough and hemoptysis associated with pulmonary edema as a result of the aggressive treatment used to eradicate the virus [40,43].

Table 1. Multisystemic pathologies associated with *Ebola virus*

System Affected	Associated Signs and Symptoms
Gastrointestinal	Anorexia, vomiting, diarrhea, pain, nausea, dysphagia, odynophagia, hemorrhage, melena, hematemesis, and hematochezia.
Neurological	Headaches, confusion, convulsions, seizure, and tinnitus.
Cardiovascular	Bilateral conjunctival injection, maculopapular rash, bleeding of mucosal tissues, and arrhythmias due to dehydration.
Respiratory	Cough with clear lungs.
Musculoskeletal	Myalgia and arthralgia.
Renal	Hematuria, renal failure due to hypotension, oliguria, and anuria.
Hepatic	Metabolic changes due to decreased yield of proteins and products.
Immune	Viral load suppresses immune response. Will have necrosis with no inflammatory infiltrates. Opportunistic infections may arise. Spleen and lymphoid tissue depletion.
Systemic	Metabolic acidosis, fever, and hypovolemic shock.

8. SCREENING AND DIAGNOSIS

The implementation of screening measures are intended to identify infected individuals with Ebola, isolate them, and prevent them from traveling in order to minimize and stop the international spread. A single lapse in detection of an infected traveler with Ebola can be devastating and may start another chain of transmission [19]. The combination of a long incubation period, nonspecific early symptoms (fever, nausea, diarrhea and weakness), and the rapid disease progression after onset, make Ebola screening challenging and therefore, it can be easily missed at border screening points [44].

The WHO elaborated a guidance document in collaboration with the USA CDC, the International Civil Aviation Organization and the International Air Transport Association to assist countries in developing exit-screening plans and to help prevent exportation of Ebola [5].

8.1 Primary Screening

Primary exit screening (Fig. 3) includes health declarations, visual inspection, and thermography to detect symptoms. It allows the

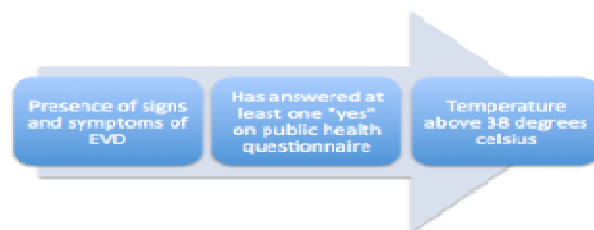
identification of travelers who may be symptomatic or who have been exposed to Ebola. The traveler is asked to complete a public health questionnaire, have his temperature measured and is visually assessed for signs and symptoms [5].

8.2 Secondary Screening

Travelers referred to secondary screening should undergo an in-depth public health interview, a medical examination conducted by healthcare professionals, and a second temperature measurement. Boarding should be denied if a traveler exhibits any clinical signs and symptoms consistent with Ebola, including a fever of 38.6°C (101.5°F), or has had any risks for Ebola exposure [5]. In addition to exit screening, countries are strongly encouraged to educate the population through extensive public health communication campaigns on prevention, risks of exposure and actions to take in case of infection.

8.3 Entry Screening

International entry screening at point of entry is not yet recommended by the WHO. Several



If traveler matches with at least one of the criteria, refer to Secondary Screening

Fig. 3. The Primary Screening Algorithm

(Adapted from WHO, [2014]) [34]

Table 2. Ebola virus diagnostic tests (Adapted from CDC, [2015]) [46]

Time of Infection	Diagnostic Tests	
Few days after onset of symptoms	✓	Antigen-capture-enzyme-linked immunosorbent assay (ELISA) testing
	✓	IgM ELISA
	✓	Polymerase chain reaction (PCR)
	✓	Virus isolation
Later in disease progression or after recovery	✓	IgM and IgG antibodies
Retrospectively in deceased patients	✓	Immunohistochemistry testing
	✓	PCR
	✓	Virus isolation

studies have shown exit screening to be more efficient than entry screening. Exit screening at international points of departure would offer greater efficiency, and might be simpler to operationalize than entry screening of all flights arriving directly from affected countries [44]. In addition, the combination of entry and exit screening has shown to have little incremental usefulness [44].

Every clinician needs to be alert to the possibility of Ebola, take thorough travel histories, and promptly isolate and test ill patients who have returned from regions at risk in the past 21 days and have symptoms consistent with Ebola [19].

8.4 Diagnosis

Diagnosis for Ebola can only be made after the onset of symptoms. It may take up to three days for the virus to reach a detectable level in the blood. It is usually accompanied by fever, which indicates the rise in circulating virus within the patient's body [45]. The following laboratory tests can be used (Table 2 above).

9. TREATMENT AND CLINICAL TRIALS

Currently, there are no FDA approved vaccines or treatments to prevent EVD in humans or cure post-exposure patients. Treatment for EVD thus far has been supportive and palliative care, as well as prevention of spread. Treatment includes fluid resuscitation, maintaining electrolytes balance, and hemodynamic monitoring initiated as early as possible following infection [47].

The recent Ebola epidemic in West Africa has accelerated clinical trials for possible vaccinations and treatment [30]. The ideal vaccine aims to provide long term protection

against all species of Ebola and strains of the Marburg virus that are pathogenic to humans [20]. Drug and vaccine candidates for clinical trials include: ZMapp, TKM-Ebola, Favipiravir, cAd3 and VSVA-EBOVGP12.

A candidate vaccine, NIAID/GSK Ebola Vaccine, was developed containing genetic material segments of the Sudan and Zaire virus species [30]. Development of the vaccine began in 2011 and the phase 1 clinical trial was to begin in 2015. Due to the Ebola outbreak in May 2014, the cAd3-EBO trial was accelerated with the phase 1 clinical trial being completed in September 2014 [16]. The Ebola virus genetic material was delivered to human cells based on a recombinant chimp adenovirus type 3 (ChAd3), but the adenovirus vector did not replicate [30]. The phase 1 clinical trial enrolled healthy volunteers between the age of 18 and 50 years. Volunteers were placed in two groups of ten each with one group receiving a low dose intramuscular injection of the vaccine and the second group receiving the same vaccine at a higher dosage. Blood samples were taken at two and four weeks post vaccination. All 20 volunteers generated anti-Ebola antibodies with the levels higher in the group who received the vaccine with the higher dose [30]. A second clinical trial was completed in the United Kingdom with 59 participants receiving a single dose of the ChAd3 vaccine at one of three dose levels. According to researchers, the ChAd3 monovalent vaccine initiated an immune response [48]. Antibody responses on ELISA were performed and showed a 100% response rate in the high-dose group and adverse events were mild and short-lived [48].

The vesicular stomatitis virus vaccine (VSVA-EBOVGP) has been shown to protect against Ebola hemorrhagic fever virus in non-human

primates when administered as a single injection [20]. It was developed at the Public Health Agency of Canada's National Microbiology Laboratory and was based on a genetically engineered version of the VSV (Vesicular Stomatitis Virus), which in humans rarely produces infections. In the vaccination, the VSV gene for the outer protein has been replaced with a segment of the gene for the outer protein of the Zaire Ebola virus species [48]. Human testing began in October 2014 and safety results were expected in March 2015 [49].

A trial is also underway for the drug cocktail ZMapp. This experimental drug made headlines in August 2014 when it was used to treat two American medical workers who had contracted the Ebola virus. The two workers made a complete recovery; however, it is unknown if the recovery was solely from the drug ZMapp [49].

ZMapp includes three monoclonal antibodies combined together that were produced in plants, specifically *Nicotiana benthamiana* [50]. Another patient treated with ZMapp in Spain died from the Ebola virus [51]. This treatment was found to protect monkeys even after being administered as late as five days following exposure to the Ebola virus [20,52]. Another study combined monoclonal antibodies consisting of 1H3, 2G4, and 4G7 (ZMAb) with Ad-IFN (adenovirus-vectored interferon-alpha) to determine if the post-exposure treatment window could be extended beyond current limits in nonhuman primates [53]. It was shown that the combination in rhesus and cynomolgus macaques could suppress viremia up to approximately 105 TCID₅₀, which would lead to survival [54]. Other drugs that are being considered for clinical trials include the influenza drug, Favipiravir, which has been approved in Japan to treat pandemic influenza and TKM-Ebola, an RNAi-based drug [47,55]. However, these trials have not yet begun and their efficacy is not proven.

Current treatment for Ebola virus disease is mainly supportive in nature. This is challenging in many settings because of the limited resources, inadequate infrastructure and lack of personal protective equipment [56]. Antibiotics to prevent and/or treat secondary bacterial infections are administered, as well as analgesics, antipyretics and antiemetic drugs [57]. Oral rehydration therapy has been preferential over intravenous fluids in order to reduce the risk of transmission. Blood products are also used to counteract hemorrhaging in patients and include packed red blood cells, platelets, fresh frozen plasma and

others [58]. Nutritional and psychosocial support as well as anxiety control is also important in reducing complications of acute illness [58].

10. CONCLUSION

Since the *Ebola virus* exists as five different known strains, a complete understanding of the virus has been an enormous task. Current research to understand the exact pathophysiology, transmission route and general nature of the current strain of the virus has been heavily funded; thus contributing to worldwide efforts to control and eradicate the disease. Understanding the routes of transmission have provided researchers and health authorities the opportunity to develop and implement disease control programs, including effective prevention, screening and diagnostic protocols. Categorizing a patient within the different phases of disease manifestation helps to accurately measure prognosis and treatment options. Once a person is suspected of contracting the Ebola virus, strict measures are set in place to control the risk of spreading the virus to any unaffected persons in contact or future contact with the individual. As there are no current FDA-approved vaccines or treatments for EVD, management of the disease is based on supportive therapy to improve recovery. This is challenging in many settings because of inadequate resources, health personnel, infrastructure and personal protective equipment. Currently, several Ebola virus vaccines are at various stages of clinical trial and some have reported strong immunologic response to the virus. Global education and effective implementation of proper preventive control measures are essential in controlling the epidemic.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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