

Global Epidemiology of EBOLA disease: a review

ABSTRACT

Ebola virus disease (EVD) is an infection with the RNA virus of the family *Filoviridae* and genus *Ebolavirus*. Five different strains of *Ebolavirus* have been recognized. EVD is a disease of humans and other non-human primates caused by ebolaviruses 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 from the disease than all other outbreaks combined. By reviewing and understanding how the early outbreaks were managed and controlled, modern-day researchers and healthcare authorities may have a better understanding of the EVD which will help in improving the surveillance quality of their health system as well as the effective management and control of the disease. As the recent strain of the *Ebolavirus* is under study since 2013, the mechanism of transmission of the virus to humans is increasingly being understood. This thus helps researchers develop preventive measures and educate countries and communities at risk on proper prevention of the disease. Protocols for effective screening and diagnosis have been developed and implemented, as well as promoted by the World Health Organization (WHO) and the Centers for Disease Control and prevention (CDC). Currently, there is no Food and Drug Administration (FDA) approved treatments or vaccinations for EVD. Clinical trials are currently ongoing with newly developed vaccines, such as the NIAID/GSK Ebola Vaccine, ZMapp and others. Since there is no cure for EVD, supportive therapy is the approved method of care for infected patients and it has been proven to be of help in alleviating and improving the recovery from the disease.

Keywords: Ebola Virus Disease, Outbreak, Surveillance, RNA virus,

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 in 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 name¹. 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 and the first to occur in West Africa. The disease 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 deaths².

This is the first EVD outbreak since its discovery to become an epidemic, as past outbreaks were brought under control within weeks. The failure to control the epidemic may be due to its occurrence in areas of extreme poverty, dysfunctional healthcare system, mistrust of government officials after years of armed conflict, and the delay in responding to the outbreak for several months¹.

The typical presentation of the symptoms of the disease usually begins within two days to three weeks of contracting the virus. It begins with fever, sore throat, muscle pain, and headaches.

This will progress to vomiting, diarrhea and rash, along with decreased function of the liver and kidneys. These are followed by Internal and external bleeding. 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, due to low blood pressure from fluid loss³.

The virus spreads by direct contact with body fluids of an infected human or animal. Semen or breast milk of a person after recovery from EVD 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 diagnosis⁴.

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 burial⁴.

No specific Food and Drug Administration (FDA) approved treatment or vaccine for the virus is available, although a number of potential treatments are being studied. Supportive or palliative efforts however, improve outcomes. This includes providing oral rehydration therapy or giving intravenous fluids, as well as treating symptoms 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 eliminate it. The ultimate goal is to eradicate the disease.

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

EBOLA EPIDEMIOLOGY

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 reported⁵. 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 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 Texas⁶. The American people were in panic situation as media outlets reported that the deadly Ebola virus was now in the country.

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 those high risk populations as well as areas needing targeted interventions, and also provide a record of disease activity for future reference⁷.

The 2013-2014 EVD outbreaks mimicked the Ebola outbreak of Zaire in 1976. The causative organism of both was *Zaire ebolavirus*, and both began in rural forest communities. Those infected with EVD reported to hospitals with symptoms resembling those of malaria, typhoid, Lassa fever or influenza. The hospital staffs were uninformed and unprepared for the virus and had contact with infected patient's blood and body fluids which further exacerbated 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 bodies of the deceased were properly disposed of by either being cremated or placed in metal caskets by following the strict guidelines enforced by the Center for Disease Control and

Prevention (CDC) for postmortem preparations. Surveillance teams headed by either a doctor or a nurse visited the 550 villages. Teams wore protective gears and brought clinical and epidemiologic forms, as well as first-aid kits, thermometers, antimalarials, antibiotics and antipyretics. Those patients encountered with symptom of fever were given medicines and advised to stay isolated from others. The most recent Ebola virus outbreak was treated very similarly to the outbreak of 1976. Priorities included the identification, surveillance and care of those infected patients and their close contacts. Also, patients were isolated, given good medical care and dead bodies were disposed of properly⁸.

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. The NYC Department of Health and Mental Hygiene (DOHMH) worked closely with local hospitals, doctors, nongovernmental organizations, community groups and city, state and federal agencies to control the current situation and reduce the outbreak from spreading. The main goals included, quickly identifying those infected with EVD, taking proper infection control precautions and transporting those who were ill to hospitals via ambulance or other emergency medical services. These 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 Airport⁸.

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, with fever over 101.5° F or 38.6° C or symptoms such as 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 case⁹.

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 elucidated¹⁰. 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 the 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 replicate¹¹.

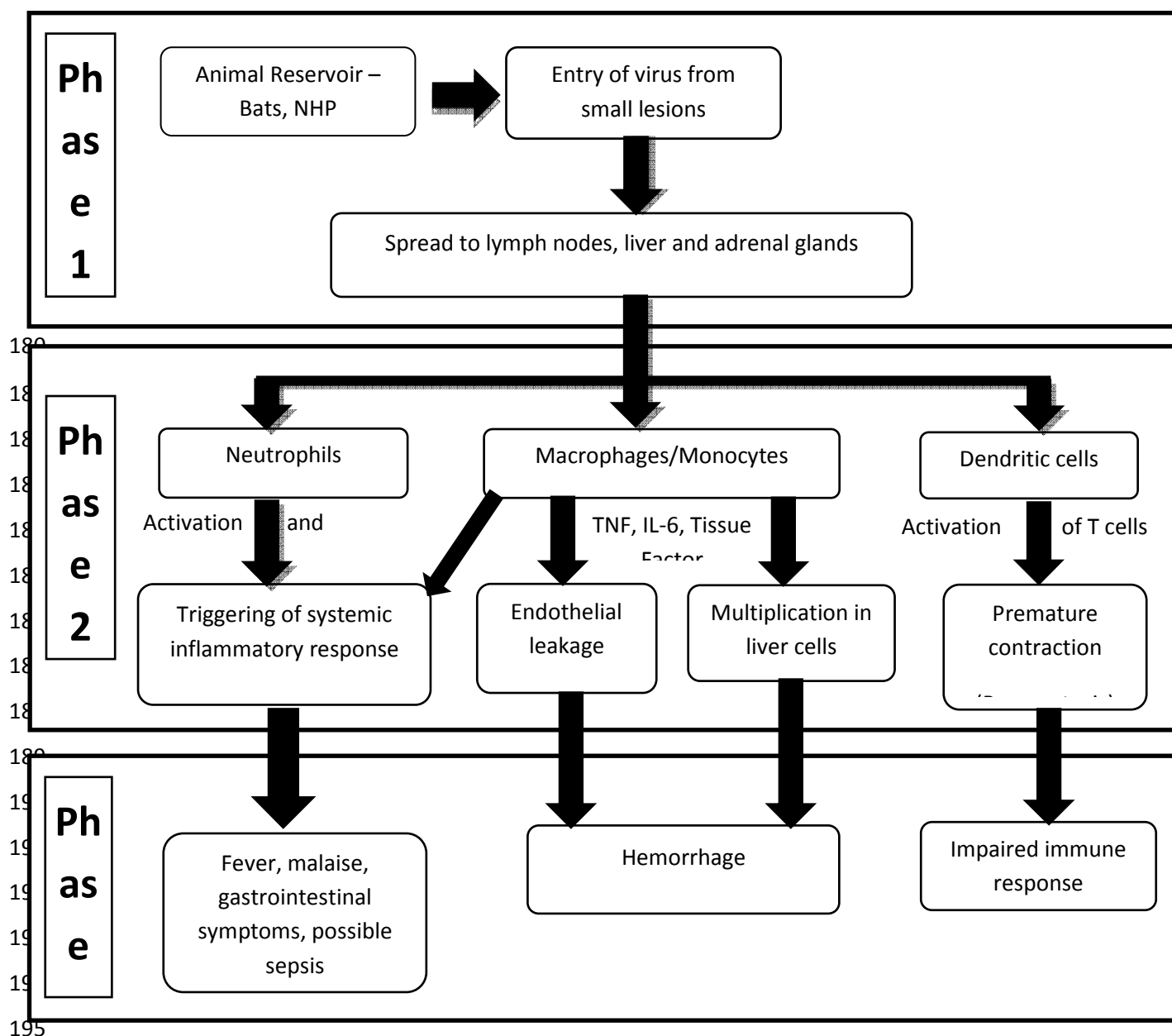
The Ebola genome codes for four virion structural proteins, respectively, VP30, VP35, nucleoprotein, and a polymerase protein. In addition, there is also a three membrane associated protein with the virus and it is referred to as, VP40, glycoprotein and VP24. The surface glycoprotein is encoded in two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

Open reading frame I encodes for a small, soluble, nonstructural secretory glycoprotein (sGP) that is readily detected in the serum of the infected hosts¹². This secretory glycoprotein then binds to neutrophil CD16b, which is exclusively expressed by human neutrophils and binds IgG in immune complexes¹⁰. 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 infection¹³. 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 cells¹². 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 disease¹⁴.

179 **Figure 1.** The Pathogenesis of *Ebolavirus* infection.



196 **Figure 1.** The flow chart depicts the pathogenesis of *Ebolavirus* infection. The mode of infection can be divided into
 197 three phases. Phase I is characterized as the transfer of the virus from an animal carrying the virus to a human, usually
 198 via small cutaneous lesions and respectively, human-to-human transmission. Phase II is denoted as the early
 199 symptomatic stage. The early symptomatic stage typically occurs between days four and ten and is the stage of
 200 infection where symptoms of viral illness appear and progressively move toward more advanced manifestations of the
 201 disease. Phase III is representative of the advanced disease, with hemorrhagic manifestations, impaired immunity, and
 202 end-organ failure¹⁰. Adapted from Kalra, S. et. al., (2014).

203

TRANSMISSION

204 The causative agent of Ebola is an RNA virus of the family *Filoviridae* and genus *Ebolavirus*.

205 Five different strains of Ebolavirus have been recognized, specifically *Zaire ebolavirus* (EBOV),

206 *Tai Forest ebolavirus* (TAFV), *Sudan ebolavirus* (SUDV), *Reston ebolavirus* (RESTV), and

207 *Bundibugyo ebolavirus* (BDBV)¹⁵. Except for RESTV, all strains are considered pathogenic to

208 humans¹⁶; however, the vast majority of past Ebola outbreaks in humans are associated with

209 EBOV, BDBV and SUDV¹⁷.

210 Human outbreaks are believed to result from direct human exposure to fruit bats or intermediate

211 infected hosts, such as non-human primates or pigs¹⁶. The hammer-head fruit bat (*Hypsignathus*

212 *monstrosus*) and the little collared bat (*Myonycteris torquata*) have been implicated as the most

213 probable reservoirs for the virus¹⁸. Contact between bats and non-human primates may occur as

214 they compete for resources during the dry season. Once the initial zoonotic transmission has

215 occurred the human epidemic can progress by direct human-to-human contact. Sequencing

216 studies conducted on 99 *Ebolavirus* genomes from 78 patients in Sierra Leone suggest that while

217 the initial transmission was zoonotic, all the remaining transmissions are likely a result from

218 human-to-human contact¹⁹. Human transmission occurs through contact with body fluids:

219 vomitus, diarrheal stool, blood, sweat, semen²⁰, saliva, breast milk, and tears². Concerning the

220 possible routes of transmission, transfer through saliva during the course of disease is particularly

221 alarming because spread can occur through intimate contact and from food sharing, mainly

222 because in Africa, eating with hands from a common plate is customary². Patients are considered

223 infectious during the symptomatic period, and remain highly infective until they enter the

224 recovery phase. Infected individuals are contagious when they begin to show symptoms and

225 without isolation each Ebola patient is estimated to infect around 1-8 additional people, leading to

226 an exponential growth with a doubling time of 20 days²¹. Large outbreaks of *Ebolavirus* are

227 commonly spread by person-to-person transmission, with caregivers both at home and in

hospitals being at higher risk²². Corpses are also viewed as highly infectious²⁰. Unsafe burials that involve washing, touching and kissing Ebola-infected bodies are major infection risks^{22, 23}. Controlling transmission requires reducing contact with bodies, body fluids of infected person and contaminated items such as clinical wastes, clothing and mattresses²⁰. Transmission does not occur through insect bite, air borne route or water sources⁴; so stopping transmission should be possible with early detection and proper management.

Information on the force of transmission of Ebola infection is critical to understanding and controlling the epidemic. The force of transmission of a disease outbreak is quantified as R , which is the average number of individuals infected by each newly infected person. If $R=1$, an outbreak is at an equilibrium, it is neither increasing nor decreasing. If $R > 1$, 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 Scientist concluded that Sierra Leone had an R value between 1.2 and 1.5, and that efforts should focus on reducing R to below 1²⁴. The key to reducing R 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-2015²⁵.

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 epidemic²⁶. 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 use of alcohol-based products, along with heat, and sodium hypochlorite (or calcium hypochlorite) has been shown to eliminate the Ebola virus from contaminated environments⁵³. Utilization of soap and water or alcohol-based hand sanitizers has been proven to disrupt the envelope that contains virulent glycoproteins which coats the Ebola virus single-stranded RNA. 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 measure to reduce the number of outbreaks includes providing guidance that encourages behavioral and cultural changes, such as safe burial methods and funeral ceremonies²². 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 personnel⁵³. 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 fluids²². 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 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 exposure⁵³. 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 bush meat. This is difficult for some areas where bush meat is the main sustenance for the local population; however, in these cases, safer slaughtering and handling are encouraged²².

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 staffs attending to either infected or non-infected patients, as well as the patient visitors, should only be in the proximity to the infected patient if they are necessary for the patient's well-being and care⁵³.

Control measures are essential to prevent the spread of the disease to other patients, healthcare workers, and visitors¹³. 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 also lacking in personal protective equipment, such as gloves, gowns and facemasks¹³. However, 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 0.05% 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 contamination⁵³.

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 viruses⁵³.

HISTORY

The Ebola virus first appeared in 1976 during two outbreaks which occurred simultaneously. First occurrence was in Nzara, Sudan and the other 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 large 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 hospital²⁶. 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)²⁷. This viral strain occurred in Gulu, Mbarara, and Masindi districts of Uganda. The virus was initially contracted by individuals who attended funerals of patients infected with the Ebola virus. Improper medical care provided to patients and lack of personal protective equipment for the medical staff contributed to the spread of the disease²⁸. From December 2002 to April 2003, the Republic of Congo was affected once again by the Ebola virus infecting 143 individuals and resulting in 89% (128 casualties) mortality rate²⁸. 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 increased number of cases. There were 264 individuals infected with the virus, resulting in a 71% mortality rate (187 casualties)²⁸. 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 Liberia²⁷ (Figure 2).



Figure 2. The 2014 Ebola Outbreak in West Africa - Outbreak Distribution Map.

Adapted from WHO, (2015).

RECENT OUTBREAK SITUATION

The 2014 Ebola virus disease (EVD) epidemic was the largest and most complex, killing more people than all previous Ebola outbreaks combined²⁹. Several West African countries were affected, primarily Guinea, Liberia, Sierra Leone with secondary cases in Mali, Nigeria, Senegal, Spain, and the United States³⁰. As of August 12, 2015, there were 27,965 reported cases of Ebola virus infection, with a 40.4% mortality rate³¹. 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^{32, 33}.

The *Zaire ebolavirus* (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 epidemic²⁹.

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 symptoms³². In March 2014, 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 rapidly³⁴.

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 US³².

CLINICAL MANIFESTATIONS

The incubation period or the duration of time from infection to when the first symptom of Ebola presents itself, commonly occurs within a 4-10 day window (may range from 2-21 days)¹¹. Affected individuals present to health care facilities on an average of 3.5 days within onset of these 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^{35, 36}. Along with such manifestations, individuals in the early stages of infection less commonly experience non-bloody watery diarrhea (5L+/day), abdominal aches, and conjunctivitis³. Gastrointestinal associated symptoms are seen

in 81% of affected individuals (nausea, vomiting, diarrhea, and abdominal pain) this typically presents 3-5 days post onset of initial symptoms³⁵. Headache, decrease in appetite, myalgia, and dysphagia tend to present 3.5-8 days post onset of initial symptoms³. 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 in a matter of hours this might be difficult to observe in the African population³⁶. Late onset of symptoms, including viral invasion of anterior chamber of the eye and seminal fluid leading to conjunctivitis and orchitis respectively may occur³⁷. 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 increase in symptoms is associated with higher risk of mortality³.

Table 1 Multisystemic Pathologies Associated with *Ebolavirus*.

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.

Death occurs within 7-12 days after the onset of initial symptoms. Approximately 40% of affected individuals will die. This is due to disease associated multi-organ failure³⁶. The three most indicative signs of lethality are presence of hiccups, hemorrhage, and shock. Presence of hiccups (15-28% of EBOV+ individuals)^{35,37}, is often a fatal sign of unknown origin; it precedes tachypnea which is almost always followed by death of the patient³⁷. Hemorrhage located in the mucosal tissues (gums, gastrointestinal, nasopharynx, and respiratory tract) and skin puncture

sites occurs 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 degrading products. This 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 mortality³⁶. Patients showing signs of hemorrhage have twelve times the risk of dying³. Approximately 50% of deceased Ebola individuals had signs of hemorrhage and 60% of patients develop shock due to hypovolemia, infection, and metabolic acidosis^{28, 11}. This typically leads to multi-organ failure and death³⁸.

The average duration of the disease is 9 days³. Cured Ebola patients are discharged if PCR is negative for the virus and if they have gone 3+ days without gastrointestinal complications³⁶. PCR may be negative for Ebola, but the virus may remain latent in tissues³⁹. Approximately, 60% of these individuals survive. Ebola survivors in recovery may later die of arrhythmias³⁶, or may potentially develop a cough and hemoptysis associated with pulmonary edema due to the aggressive treatment applied to eradicate the virus. Two weeks following initial symptoms, Ebola survivors may regain their appetite; however, the arthralgia may continue indefinitely³⁹.

SCREENING AND DIAGNOSIS

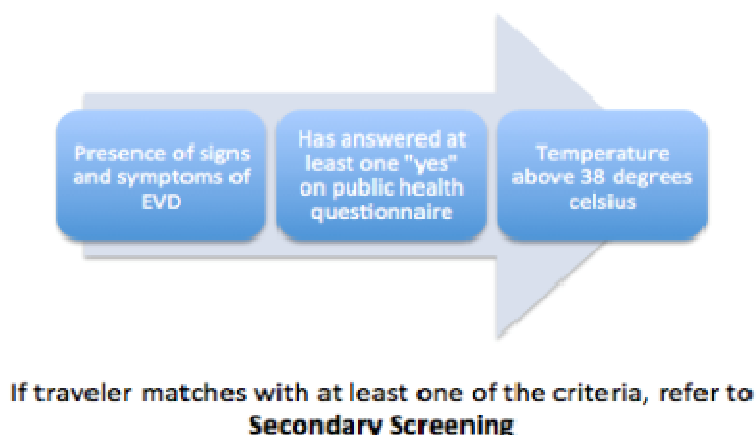
The implementation of screening measures are intended to identify infected individuals with Ebola, isolate them, and prevent them from traveling in order to minimize and stop the international spread. A single lapse in detection of an infected traveler with Ebola can be devastating and may start another chain of transmission¹⁸. 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 points⁴⁰.

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.

Primary Screening:

Primary exit screening (Figure 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 symptoms⁵.

Figure 3. The Primary Screening Algorithm. (*Adapted from WHO, (2014).*)



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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 101.5° F or 38.6° C, or had any risks for Ebola exposure⁵. 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.

Entry Screening:

International entry screening at point of entry is not yet recommended by WHO. Several 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 countries⁴⁰. In addition, the combination of entry and exit screening has shown to have little incremental usefulness⁴⁰.

Every clinician needs to be alert to the possibility of Ebola, to be able to take thorough travel history, and promptly isolate and test ill patients who have returned from regions at risk in the past 21 days and have symptoms consistent with Ebola¹⁸.

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 body⁴². The following laboratory tests can be used (Table 2):

Table 2. Ebola Virus Diagnostic Tests. *(Adapted from CDC, (2015)).*

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

TREATMENT AND CLINICAL TRIALS

Currently, there are no FDA approved vaccines to prevent EVD in humans or treatments to cure post-exposure patients. Treatment for EVD thus far has been supportive and palliative care, as well as prevention of transmission. Treatment includes fluid resuscitation, maintaining electrolytes balance, and hemodynamic monitoring initiated as early as possible following infection⁴³.

The recent Ebola epidemic in West Africa has accelerated clinical trials for possible vaccinations and treatment ²⁶. “The ideal vaccine that meets all needs would, with a single administration, rapidly confer long-term protection with little or no *filovirus* viremia against all species of Ebola that are pathogenic in humans, as well as the diverse strains of Marburg Virus”¹⁹. Drug and vaccine candidates for clinical trials include: ZMapp, TKM-Ebola, Favipiravir, cAd3 and VSVΔ-EBOVGP12.

A candidate vaccine, NIAID/GSK Ebola Vaccine, was developed containing genetic material segments of the Sudan and Zaire virus species²⁶. Development of the vaccine began in 2011 and the phase 1 clinical trial was to begin in 2015. The cAd3-EBO trial was accelerated; however, because of the Ebola outbreak in May 2014, the phase 1 clinical trial was completed in September 2014¹⁵. 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 replicate²⁶. 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 dose²⁶. 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, against EBOV, was immunogenic at the doses tested”⁴⁴. Antibody responses on ELISA were performed and showed a 100% response rate in the high-dose group and adverse events were mild and short-lived⁴⁴.

The vesicular stomatitis virus vaccine (VSVΔ-EBOVGP) has been shown to protect against Ebola hemorrhagic fever virus in non-human primates when administered as a single injection¹⁹. 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 species⁴⁴. Human testing began in October 2014 and safety results were expected in March 2015⁴⁵.

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 ZMapp⁴⁵. ZMapp is three monoclonal antibodies combined together that were produced in plants, specifically *Nicotiana benthamiana*⁴⁶. Another patient treated with ZMapp in Spain died from the Ebola virus⁴⁷. This treatment was found to protect monkeys even after being administered as late as five days following exposure to the Ebola virus^{19, 48}. 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 primates⁴⁹. It was shown that the combination in rhesus and cynomolgus macaques can suppress viremia up to approximately 105 TCID50, which would lead to survival⁵⁰. 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^{43, 51}. 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 equipment⁵². Antibiotics to prevent and/or treat secondary bacterial infections were administered, as well as analgesics, antipyretics and antiemetic drugs, as needed⁵³. Oral rehydration therapy has been preferential over intravenous fluids, in order to reduce the risk of transmission. Blood products were also used to counteract hemorrhaging in patients and these included packed red blood cells, platelets, fresh frozen plasma and others⁵⁴. Nutritional and psychosocial supports as well as anxiety control are also important in reducing complications of acute illness⁵⁵.

CONCLUSION

As the *Ebolavirus* exists as five different known strains, it is clear that a complete understanding of the virus has been quite an enormous task over the last 40 years. Current research to understand the exact pathophysiology, transmission route and general nature of the current strain of the virus has been heavily funded, and thus has contributed to the worldwide effort towards controlling and eradicating the disease. As each strain varies significantly, the understanding of the route of infection is essential in the control of this disease. Researchers concluded that the recent strain of the virus is transmitted via bodily fluids, such as vomitus, diarrhea, blood, sweat, and semen. Understanding the routes of transmission has provided researchers and health authorities the opportunity to develop and implement disease control programs, which include effective prevention, screening and diagnostic protocols. Proper implementation of a disease prevention protocol in at risk areas is essential to reaching the eradication goal. As discussed earlier, there are numerous highly advanced and expensive strategies for preventing infection

with the virus as well as proper personal hygiene when working with infected patients or the remains of the deceased. These are the most useful measures in minimizing further risk and exposure. Categorizing a patient within the different phases of disease manifestations after diagnosis 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. Antibiotics to prevent and/or treat secondary bacterial infections are being used along with analgesics, antipyretics and antiemetic drugs, as needed. Oral rehydration has been the preferred route of rehydration in patients, in order to decrease risk of transmission. Furthermore, blood products are also being used to counteract hemorrhaging in patients. Nutritional, psychosocial support and anxiety control are all very important in order to reduce complications of acute illness. Currently, several Ebola virus vaccines are at various stages of clinical trial and some have reported strong immunologic response to the virus. Hopefully, in the near future, the vaccine for Ebola virus will be realized. Global education and effective implementation of proper preventive control measures are essential in controlling the epidemic.

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