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Ebola Virus Disease in 2015: An Epidemiological History

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Ebola Virus Disease in 2015: An Epidemiological History

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An abstract of
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Abstract

Ebola Virus Disease in 2015: An Epidemiological History
By Lauren Guest

This thesis explores the epidemiological history of Ebola Virus Disease (EVD) since it was discovered in 1976. By far the largest ever epidemic of EVD appears to be drawing to a close in West Africa. However, it has entered the most difficult stage—that of total elimination of all Ebola cases in the human population. This is difficult given the remoteness of many communities, their poor access to health services and transportation concerns. However, the region contains more hospital beds, laboratories and health staff than it ever did prior to the epidemic—this fact, combined with the treatment and vaccine trials currently underway in areas where weekly case numbers are still high, finally hints at an end to an epidemic that infected over 25,000 people.

The West African Ebola epidemic had devastating consequences on the region both in terms of lives lost and economic impacts. Therefore, it is even more imperative that the lessons learned should serve to reduce the magnitude and scope of future Ebola and other infectious disease epidemics. These include: 1) aggressive treatment including life-support measures can improve survival in some patients, 2) the importance of an immediate and efficient response by UN agencies, and 3) increased awareness of the importance of improving health systems in low resource countries to prevent and control future epidemics.

Researchers who worked on an Ebola epidemic in Uganda several years prior to the West African epidemic concluded that there was a major need for improved surveillance, reporting and diagnostics to prevent further epidemics of this deadly virus. Their advice went unheeded, but perhaps the devastation of many West African communities will allow appropriate distribution of financial and personnel resources to prevent such an epidemic in the future. The West African Ebola response has fostered new partnerships between pharmaceutical companies, researchers and governmental organizations to develop and push through promising treatment and vaccine candidates for Ebola. Although many of these will come too late to be of much use in the current epidemic, they have the potential to protect high-risk communities in Central and West Africa from future Ebola epidemics.

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Introduction

An unprecedented epidemic of Ebola Virus Disease (EVD) is raging in Guinea, Sierra Leone and Liberia. Imported cases have occurred in Mali, Senegal, Nigeria and the United States. The first Ebola case acquired on US soil as a result of improper use of personal protective equipment by a healthcare worker threw Texas and other parts of the United States into chaos as irrational fears of sustained transmission gripped the US. It's been a disheartening time to be American, as racism and discrimination have been wielded as a weapon of ignorance and fear—Africans with recent travel to African countries unaffected by the Ebola epidemic have been denied entry to schools and work; it's been a remarkably worse time to be a West African.

The first infection of an American healthcare worker on American soil did, however, force Americans to acknowledge the epidemic and call for more to be done to end its burn through Sierra Leone, Liberia and Guinea. A stronger global response was launched to assist Medicins Sans Frontieres (MSF) and United Nations (UN) agencies (primarily WHO). The United States Centers for Disease Control and Prevention (CDC) became a major player in the West African response and received $6.18 billion in emergency funds for immediate and long-term response efforts (Office of the Press Secretary, 2014). The major role the United States played in the response combined with the effect of the first imported case and the two subsequent infections acquired on US soil drew intense fascination to a hemorrhagic fever that was previously unknown to most Americans.

Since Ebola Virus was first isolated and identified in 1976, it has resulted in sporadic epidemics—mainly in Uganda, South Sudan and the Democratic Republic of the Congo—all of which were contained fairly quickly and did not spread from their rural origins. Neither a

specific treatment nor a tested vaccine has been developed. The 2014 epidemic made the jump from rural to more densely populated settings and this allowed transmission at rates never before experienced with this pathogen. The ongoing epidemic has caused more than ten times the total number of human Ebola infections recorded since its discovery and has significantly increased our knowledge and understanding of the epidemiology and clinical picture of Ebola Virus Disease.

Perhaps even more importantly, it has demonstrated the woeful inadequacy of many nations' healthcare systems. Three months passed between the first case of Ebola in Guinea and notification of Guinea's Ministry of Health of a hemorrhagic fever epidemic with an exceptionally high case fatality rate in the Southeastern region. Those critical three months allowed the disease to spread and cross the border into Liberia and eventually Sierra Leone before the international world identified the pathogen causing the epidemic as Ebola and attempted to mobilize resources to combat its spread. It is not difficult to imagine an entirely different scenario in which the first few cases of an unknown hemorrhagic fever with a high case fatality rate would be treated by nurses in a rural clinic or hospital rather than by a rural community health worker. This, most likely, would have resulted in immediate notification of the problem to Guinea's Ministry of Health. This would have started a crucial chain of reaction that brought national and/or foreign health professionals in to collect samples from patients in order to isolate the pathogen and immediately conduct contact tracing to stem the spread of the disease.

Pathogens like Ebola, with high case fatality fates and no known treatments, are a significant reason behind the recent push for investing in health infrastructure and increasing public health capacity in low resource countries. Barack Obama's Global Health Initiative joins a

multitude of global health programs that have made health systems strengthening a top priority in the next few decades. This goal stems from recent acknowledgement that inadequate health systems have hampered efforts to eradicate and reduce disease burdens globally. An investment in Malaria diagnostics may help reduce the length of time between onset of symptoms and the beginning of treatment—potentially leading to better health outcomes—but it cannot ensure that there is a clinic or hospital for that patient to seek and receive care. Investments in the building of hospitals, rural clinics, health laboratories, disease surveillance systems and the training of health workers expands access to care and improves health outcomes for the long-term.

Investments in Guinea's healthcare system would have had several opportunities to change the tide in this epidemic. Instead, the Ebola epidemic spilled into Liberia and Sierra Leone with thousands of cases in a region that collectively had a 1,126-hospital bed capacity—only ¼ of what is needed ("Ebola: Mapping the Outbreak", 2014). The cost has been catastrophic—both economically and in lives lost. Over USD $8 billion has already been allocated for the Ebola response and billions more have been requested in order to bring an end to the epidemic ("Killer cost of Ebola," 2014). Imagine how many hospitals could have been built or healthcare workers trained with the same funds.

If low resource countries do not have the laboratory and treatment capacity to diagnose known or emerging infectious diseases and prevent them from spreading, then they have the potential to become threats to our own health care systems. In his 2001 Nobel Peace Prize acceptance speech, Kofi Annan argued, "Today's real borders are not between nations, but between powerful and powerless, free and fettered, privileged and humiliated. Today, no walls can separate humanitarian or human rights crises in one part of the world from national security crises in the other" (2001). The same logic also applies to diseases and the current Ebola

epidemic has demonstrated once again the ease and swiftness with which a pathogen spreads through a city, crosses arbitrary borders and jumps from one continent to another through a vastly complex web of global transportation systems.

This thesis aims to provide a background on hemorrhagic fevers in general, Ebola Virus Disease specifically, a detailed description of the West African epidemic and the global response, appropriate prevention and infection control measures in both high and low income settings, the role of politics and the media in the current Ebola response, treatment and vaccine possibilities, ethical issues in Ebola vaccine and treatment research, and ultimately how the 2014 Ebola epidemic demonstrates the importance of current and future global health systems strengthening efforts.

Chapter 2: Description & History of Hemorrhagic Fevers

Viral Hemorrhagic Fever (VHF) is a loose term used to describe a widely varied group of viruses capable of causing serious human disease affecting multiple body organ systems that result in internal hemorrhaging and sometimes death. Generally, there are four virus families considered to contain VHFs: *Arenaviridae*, *Filoviridae*, *Bunyaviridae*, and *Flaviviridae* (Centers for Disease Control and Prevention [CDC], 2013). However, the recent discovery of Bas-Congo Virus (BASV) in 2012 added *Rhabdoviridae* as a fifth family capable of causing VHFs (Ergonul et al 2014).

CDC has identified several characteristics that all VHFs have in common including: 1) they are Ribonucleaic Acid (RNA) viruses with a lipid coating, 2) they have an animal reservoir and are limited by the geographic distribution of that reservoir, 3) no VHF has a natural reservoir in humans, 4) epidemics are sporadic, not easily predictable and happen when a spillover occurs between the animal reservoir and a human host, and 5) there are no established cures or treatment methods other than supportive care (CDC, 2013). Most VHFs are zoonotic infections, which means they survive and replicate in an animal reservoir. The most common VHF reservoirs are rodents and arthropods such as: cotton rats, deer mice, ticks and mosquitos—however, bats are thought to be potential reservoirs of certain hemorrhagic fevers (Howard, 2005; CDC, 2013). In general, symptoms of VHFs include: fatigue, fever, weakness, muscle aches and various forms of internal and external hemorrhaging. However, the individual symptoms vary widely for each virus and severity often depends upon the viral load (Howard, 2005). Hemorrhagic fever infections tend to be much more serious in pregnant women and generally results in spontaneous abortion and the death of the fetus (Howard, 2005). The five

viral families and their corresponding VHFs are detailed below including a short history, epidemiology and clinical picture of the disease.

Arenaviridae

Arenaviridae is a viral family mainly responsible for rodent-transmitted diseases in humans (CDC, 2013). The first Arenavirus, lymphocytic choriomeningitis virus, was identified in St. Louis in 1933 and the family now contains 27 known viruses (Howard, 2005; CDC, 2013). The family is split into two groups known as the Old World and New World Arenaviruses based on geographic and genetic distinctions (Howard, 2005). Of the 27 identified arenaviruses, 6 are known to cause hemorrhagic fever in humans, a couple cause non-hemorrhagic illnesses in humans and the remaining have only been isolated in animals and do not appear to cause disease in either animals or humans. The six arenaviruses that cause hemorrhagic fever in humans include: Lassa fever virus, Junin virus, Machupo virus, Guanarito virus, Lujo virus and Sabia virus.

Lassa Fever Virus

Lassa virus was first discovered in 1969 when it caused a severe infection in an American nurse working in Lassa Township, Nigeria. She died several days later and two secondary cases occurred among hospital staff directly involved in treatment—one of the two recovered after being transferred to a US hospital and receiving supportive care (Howard, 2005). The virus was isolated from the serum of the female nurse who recovered from the disease and named by the Yale Arbovirus Unit in Connecticut (Howard, 2005). Epidemics occur every year in endemic countries in West Africa including: Nigeria, Sierra Leone, Guinea and Liberia. Cases and serologic evidence of infection have also been reported in Mali, Burkina Faso, Cote d'Ivoire,

Ghana, Togo and Benin (CDC, 2013). The virus's natural reservoir is the multimammate rat that is common in West, Central and East Africa. The rat excretes the virus in both urine and feces long-term after the initial infection and easily transmits it to humans through close proximity to homes and food storage (CDC, 2013). Most infections occur through ingestion of contaminated food or water or by inhalation. However, some cases occur as a result of direct contact with the body fluids of an infected rat; person-to-person transmission can also occur (CDC, 2013).

The CDC estimates an annual case count of 100,000-300,000 in the endemic region resulting in 5,000 deaths per year. (2013). The large range of this estimate is due to nonexistent or severely under functioning surveillance systems and deficient laboratory capacity to detect and confirm cases in endemic countries. It is estimated that up to 80% of cases of Lassa fever are subclinical infections, meaning that the patients do not experience any significant symptoms of the disease (Howard, 2005). The other 20% of cases present with symptoms such as: fever, sore throat, cough, stomach pain, back pain, muscle pain, vomiting and hemorrhaging of the gums, eyes or nose. The incubation period is 3-21 days; symptoms last for several weeks and many patients that recover from clinical disease experience long-term side effects including fatigue, hair loss and deafness (Heymann, 2014). Early treatment with the anti-viral drug Ribavirin and supportive care has been shown to be effective in increasing patient's chances of recovery (Howard, 2005). The case fatality rate among those who manifest clinical disease varies from 15-50% depending on the size of the epidemic and available healthcare services. However, the case fatality rate of all Lassa infections (clinical and subclinical) is closer to 1% (CDC, 2013).

Junin Virus

Junin virus causes Argentine Hemorrhagic Fever (AHF) and was first isolated in 1958 in Buenos Aires (Howard, 2005). The natural host of the Junin virus is the corn mouse—epidemics tend to be seasonal and take place around the corn harvest between February and May. The endemic region spreads north and west of Buenos Aires putting approximately 1/5th of Argentineans at risk of infection, especially agricultural workers who come in direct contact with the mice and their droppings (Howard, 2005). Transmission routes have not been established, however, it is believed that ingestion and inhalation are the main paths (CDC, 2013). Annual epidemics occur in Argentina resulting in 100-800 cases during the corn harvest, however, cases also occur throughout the rest of the year (Howard, 2005). The incubation period ranges from 7-16 days and cases present with symptoms such as: chills, headache, weakness, muscle pain, nausea, fever, and swelling of the face. In more severe cases, the disease progresses to hemorrhaging from the nose and mouth and the case fatality rate ranges from 3-20% (Howard, 2005). Although subclinical infections do occur, they do not play a major role as in Lassa fever. Ribavirin is thought to increase chances of survival, but serum transfusions from recovered patients with Junin virus antibodies has been the most effective treatment (CDC, 2013). Several vaccines have been developed and the current vaccine Candid No. 1 is recommended for all agricultural workers in endemic regions (CDC, 2013).

Machupo Virus

Machupo virus causes Bolivian Hemorrhagic Fever (BHF) and was first identified in Northeastern Bolivia in 1959 (Howard, 2005). Annual epidemics occurred for several years and then slowly tapered off—human infections are now reported very rarely. As with AHF, BHF outbreaks coincided with the local corn harvest from March to June as contact with the vole

reservoir, *Calomys callosus*, increased significantly (Howard, 2005). The clinical manifestation of the disease is highly similar to AHF and begins as an influenza-like illness with fatigue and weakness. As the disease progresses, further symptoms include stomach pain, tremors, anorexia and severe limb pain (CDC, 2013). Approximately 1/3 of patients develop hemorrhaging, especially from the nose, gums and uterus. The incubation period is 1-2 weeks; subclinical infections are rare and recovery from the disease can take several weeks. Transmission is thought to occur through the ingestion of food and water contaminated by an infected vole (CDC, 2013). Case fatality rates have ranged from 5-30% during outbreaks. Treatment is mainly supportive care; no significant studies have been conducted to indicate whether Ribavirin or plasma with antibodies from a recovered case improve treatment outcomes (Howard, 2005).

Sabia Virus

Sabia virus causes Brazilian Hemorrhagic Fever and was first isolated in 1990 during the autopsy of an agricultural worker from just outside Sao Paulo, Brazil (Howard, 2005). The reservoir of the Sabia virus has never been identified, but it is assumed to be a rodent of some kind (CDC, 2013). Since its discovery, only three confirmed cases of Brazilian Hemorrhagic Fever have occurred and two were among laboratory workers exposed to the virus. Little is known about the clinical presentation of the disease but it is thought to be similar to AHF (Howard, 2005). An American laboratory worker exposed to the virus was successfully treated with Ribavirin but no further studies have been conducted to determine the treatment efficacy. Transmission is assumed to be mainly through ingestion and inhalation (CDC, 2013).

Guanarito Virus

Guanarito virus causes Venezuelan Hemorrhagic Fever (VHF) and was first identified in 1990 when an epidemic occurred in Guanarito, Venezuela (Howard, 2005). As with AHF and

BHF, most cases occurred among agricultural workers and the reservoir was identified as the short-tailed cane mouse (CDC, 2013). Each year, the incidence peaks between the harvest months of November to February and over 700 confirmed and probable cases were reported between 1990 and 2014. Ingestion and inhalation are the major transmission routes, although person-to-person spread is possible. VHF infection presents very similarly to AHF and BHF, however, diarrhea and pharyngitis are more commonly reported in VHF cases than with other South American hemorrhagic fevers (Howard, 2005). The incubation period ranges from 6-14 days and case fatality rates range from 15-30%. The presence of antibodies in the endemic region suggests there may be a significant number of subclinical infections, meaning that the case fatality rate is probably lower than previously reported (Howard 2005; CDC, 2013). Treatment for VHF is supportive care.

Lujo Virus

Lujo virus was first identified in 2008 when a case of an unknown hemorrhagic fever occurred in a female patient from Lusaka, Zambia. She was airlifted to a hospital in Johannesburg and four secondary cases occurred among healthcare workers who were involved in her treatment (CDC, 2013). This is the only known human epidemic and it resulted in an 80% case fatality rate. Neither the reservoir nor the endemic region of the Lujo virus is known. The only person who survived was treated early on with Ribavirin; however, no further studies on the antiviral's effectiveness against Lujo have been conducted (CDC, 2013). The incubation period is estimated to be 1-2 weeks and symptoms of the known cases included: facial swelling, rash on the face and trunk, sore throat, and diarrhea. Hemorrhaging was markedly not a prominent feature of the disease among the five known cases (CDC, 2013).

Bunyaviridae

Bunyavaridae is a large viral family containing over 300 distinct viruses that are usually transmitted through an arthropod vector such as mosquitos, ticks and sandflies (Howard, 2005). However, Hantaviruses—which are the causative agent of several hemorrhagic fevers—are the exception to this rule as they do not have an arthropod vector and are transmitted through rodents (CDC, 2013). There are five bunyavirus diseases that cause hemorrhagic fever in humans: Rift Valley fever, Congo-Crimean hemorrhagic fever, Hemorrhagic fever with renal syndrome, Nephropathia endemica and Hantavirus pulmonary syndrome.

Rift Valley Fever

Rift Valley Fever (RVF) is caused by the Rift Valley fever virus and was first identified in Kenyan livestock in the early 1900s (Howard, 2005). Although the virus primarily infects livestock, it is capable of causing severe human disease. The virus is endemic to most of sub-Saharan Africa and causes frequent epizootics in livestock and sporadic epidemics in humans (Howard, 2005; CDC, 2013). More recently, epidemics have occurred in Saudi Arabia and other Middle Eastern countries as a result of the importation of infected livestock. *Aedes* and *Culex* mosquitos are both a reservoir and a vector for the virus and transmission to livestock and humans often occurs through the bite of an infected mosquito (Heymann, 2014). Direct contact with the blood and/or milk of infected animals has also been established as an important transmission route for humans (CDC, 2013). Epidemics are more common during the rainy season when mosquito populations grow rapidly. Changes in weather patterns and trade have allowed the endemic region of the virus to grow from sub-Saharan Africa to North Africa and the Arabian Peninsula (WHO, 2014). Rift Valley fever virus poses a major threat to nation's economies as the decimation of large numbers of livestock from RVF epizootics has had

crippling effects on African and Arabian countries in the past (Howard, 2005). Incidence rates have not been established in livestock or in humans but major outbreaks occur in livestock every couple of years that spillover to humans. The largest epidemic recorded occurred in Egypt from 1977 to 1978 where an estimated 200,000 people were infected resulting in 594 deaths.

The incubation period of the virus is 2-6 days and a large proportion of people who are infected will not show any symptoms of the disease (Heymann 2014; Howard, 2005). In patients who develop clinical infection, symptoms include: fever, weakness, dizziness and back pain. In more severe infections, patients can develop ocular disease, encephalitis and hemorrhaging (Howard, 2005). Although hemorrhagic fever occurs in only 1% of all RVF cases, the case fatality rate for these patients is 50% (Howard, 2005). The overall case fatality rate associated with RVF is closer to 1% (CDC, 2013). Treatment includes supportive care; it is unknown whether Ribavirin is effective against the virus. A vaccine has been developed but it has not been licensed nor used except in high-risk individuals CDC, 2013). A vaccine has also been developed to prevent disease in livestock and is usually used to prevent further spread when an epizootic is identified.

Congo-Crimean Hemorrhagic Fever

Congo-Crimean Hemorrhagic Fever (CCHF) is caused by the Nairovirus and infects both humans and animals (Howard, 2005). The virus was first identified in 1944 in Crimea and was followed by a major epidemic in the Congo in 1956 (Howard, 2005). The reservoir of the virus includes dozens of species of ticks but transmission most often occurs through the Hyalomma tick. CCHF is the most widespread tick-borne virus and is endemic to Africa, Eastern Europe, Asia and the Middle East. Hundreds of laboratory confirmed cases occur worldwide each year and thousands are considered to go unreported. The tick infects livestock and other domestic

animals and transmission to humans most often occurs through direct contact with the blood of infected animals, but can also occur through the bite of an infected tick (CDC, 2013).

The incubation period is 1-14 days depending on the mode of transmission and subclinical infections are rare (Howard, 2005; WHO, 2014). The first symptoms of the disease include: fever, muscle pain, headache, back pain, dizziness and sensitivity to light. Severe cases may develop confusion, mood swings, bleeding under the skin, liver failure or pulmonary failure. The case fatality rate is 30-40%. Treatment includes supportive care and use of the antiviral Ribavirin (WHO, 2014). No vaccines have been developed for use in humans or animals.

Hemorrhagic Fever with renal syndrome

Hemorrhagic Fever with Renal Syndrome (HFRS) includes several diseases that are caused by different Hantaviruses including: Hantaan, Seoul, Dobrava, Saaremaa and Puumala (CDC, 2013). Due to the extensive range of these viruses, HFRS is endemic around the world; however, each of these viruses has a specific reservoir and region. Hantaviruses are transmitted through rodents and transmission occurs to humans through exposure to the virus shed in the urine and feces of infected animals (Howard, 2005). In China alone, an estimated 100,000-250,000 cases occur each year.

The Incubation periods of Hantaviruses resulting in HFRS are usually 1-2 weeks and initial symptoms include: headache, stomach pain, back pain, fever, chills, and nausea (Howard, 2005). Severe infections are more common in cases caused by Hantaan and Dobrava viruses and patients can go into shock and develop kidney failure (CDC, 2013). The case fatality rate ranges from 1-15% depending upon the virus causing the underlying infection. Treatment includes supportive care and use of the antiviral Ribavirin (Heymann, 2014; CDC, 2013).

Hantavirus Pulmonary Syndrome

Hantavirus Pulmonary Syndrome (HPS), similarly to HFRS, includes several diseases that are caused mainly by two Hantaviruses—Sin Nombre and Andes. The reservoir of the Sin Nombre virus is the deer mouse and it is endemic to the Western and Central regions of the United States and Canada (CDC, 2013). The reservoir of the Andes virus is the long-tailed rice rat and it is endemic to Argentina and Chile. Transmission occurs through ingestion and inhalation of particles contaminated with the feces and urine of infected rats (CDC, 2013). There are an average of 30 cases of HPS confirmed in the US each year and small, geographically confined epidemics are reported annually in most South American countries.

The Incubation period has not been definitively determined, however a range of 1-5 weeks is generally accepted (Heymann, 2014; Howard, 2005). Symptoms of HPS include: fever, fatigue, muscle aches, headaches, stomach pain, diarrhea and dizziness. Severe infections lead to coughing, shortness of breath and fluid in the lungs. The case fatality rate is 38% and the only treatment method is supportive care. (Howard, 2005).

Flaviviridae

Flaviviridae is a viral family that causes a significant proportion of morbidity and mortality from infectious disease globally (CDC, 2013). Flaviviruses are vector-borne diseases transmitted through ticks and mosquitos (Howard, 2005). There are two flaviviruses that cause hemorrhagic fever in humans: Dengue and Yellow Fever.

Yellow Fever

Yellow Fever is one of the oldest viruses known to man and it infects humans as well as primates (Howard, 2005). It's name stems from the jaundice or yellowing of the skin that it causes in a proportion of patients. The virus is transmitted to humans through the bite of infected *Aedes* and *Haemogogus* mosquitoes (Heymann, 2014). The World Health Organization estimates an average of 200,000 cases per year resulting in 30,000 deaths globally (WHO, 2014). Yellow Fever virus is endemic in many African and Latin American countries; it has been eliminated from North America and Europe through effective vector control methods (Heymann, 2014).

The incubation period of Yellow Fever is 3-6 days and initial symptoms include: fever, muscle pain, backache, headache, loss of appetite, nausea and vomiting. Severe infections enter the toxic phase and develop jaundice due to liver damage, hemorrhaging from the mouth, nose eyes and stomach (Howard, 2005; Heymann 2014). Among those that enter the toxic phase, there is a 50% case fatality rate. The overall case fatality rate is estimated at 5-10% (WHO, 2014). Treatment includes supportive care and careful monitoring of body system functioning. A highly effective live vaccine has been in use since the 1930s and is recommended in travelers to endemic regions and administered in childhood to populations living in endemic regions (Heymann, 2014; CDC, 2013).

Dengue Fever

Benjamin Rush first described Dengue Fever, caused by the Dengue Fever virus, during a major outbreak in Philadelphia in 1780 (Howard, 2005). Dengue is often referred to as Breakbone Fever due to the severe muscle aches that often characterize infection. The reservoir of the Dengue virus is *Aedes* mosquitoes, with *Aedes aegypti* being the most common species. Infection occurs through the bite of an infected female and there are five unique serotypes of the

Dengue Fever virus (Heymann, 2014). The virus is endemic to most tropical and sub-tropical regions worldwide and the World Health Organization estimates 50-100 million infections occur each year (WHO, 2014).

The incubation period for Dengue Fever is 4-10 days and symptoms include: fever, headache, muscle pain, joint pain, nausea, vomiting, and a rash. Severe infections with Dengue Fever, referred to as severe Dengue, can lead to Dengue Shock Syndrome (DSS) or Dengue Hemorrhagic Fever (DHF) causing an accumulation of fluids in the body, respiratory distress, bleeding from the gums, blood in vomit and restlessness (Heymann, 2014). Approximately 5% of all cases of Dengue infection lead to severe disease resulting in DSS or DHF—risk of severe disease is greater in children, those with chronic illnesses and those with previous infection with a different strain of the virus. The total case fatality rate is estimated at 2.5%, but with the high global burden of disease this leads to significant morbidity and mortality (WHO, 2014). Treatment includes supportive care and while no vaccine has been developed to date, several vaccines are currently being tested (WHO, 2014).

Rhabdoviridae

Rhabdoviridae is a viral family that infects animals, humans and plants (Ergonul et al, 2014). The only known rhabdovirus that causes hemorrhagic fever in humans is Bas-Congo virus (Grard et al, 2012).

Bas-Congo Virus

Bas-Congo Virus (BCV) was discovered in 2009 outside Kinshasa in the Democratic Republic of the Congo. Only three cases have been documented and the virus is thought to be

spread through direct contact with the body fluids of an infected case since one of the cases occurred in a healthcare worker involved in the treatment of the other two cases (Grard et al, 2012; Ergonul et al, 2014). The reservoir of the virus is unknown and symptoms include: fever, weakness, fatigue, nausea, vomiting, diarrhea, stomach pain and hemorrhaging. Of the three known cases, two died from the disease, which gives an estimated case fatality rate of 67% (Grard et al, 2012).

Filoviridae

Filoviridae contains only two viruses—Marburg and Ebola—both of which infect human and nonhuman primates (Howard, 2005; CDC, 2013). This is the only viral family where all of its members are known to cause hemorrhagic fever in humans. Filoviruses are very similar to Rhabdoviruses and a few important differences resulted in the creation of this viral family when Marburg virus was identified (Howard, 2005). The epidemiologic features of Marburg virus are detailed below and the entire next chapter is dedicated to the epidemiologic features of the Ebola virus.

Marburg Virus Disease

Marburg Virus Disease results from infection with one of two Marburg viruses—Marburg or Ravn—and causes infection in humans and nonhuman primates. It was first identified in 1967 when it caused three simultaneous epidemics in Europe among laboratory employees working on the production of cultures for Polio vaccine (Howard, 2005). The infections were traced back to employees who had direct contact with the body fluids of a shipment of vervet monkeys from Uganda and a total of 31 cases were identified (Heymann, 2014). Since its discovery, sporadic epidemics of Marburg virus have occurred in Kenya, South

Africa, Angola, Uganda, the Democratic Republic of the Congo and imported cases have occurred in Russia, the US and the Netherlands. These epidemics have all been relatively small and only 465 laboratory confirmed cases of Marburg Virus Disease have been identified since its discovery in 1967 (CDC, 2014). The reservoir of the Marburg virus is the African fruit bat and transmission occurs through inhalation and ingestion of bat droppings from infected animals (CDC, 2014). Direct contact with the infected blood of fruit bats and primates during the killing and food preparation process is also considered to be an important transmission route. The virus is thought to be endemic to most of sub-Saharan Africa (Heymann, 2014; CDC 2014).

The incubation period of Marburg virus is 2-21 days and initial symptoms include fever, fatigue, muscle pain and headache followed by a sore throat, vomiting, diarrhea and a rash. The next phase of Marburg disease often involves renal failure, multisystem failure and internal hemorrhaging (Howard, 2005; CDC 2014). The case fatality rate of Marburg virus outbreaks has been between 25 and 80%. Of all laboratory confirmed cases, the case fatality rate is 80% (CDC, 2014). Treatment includes supportive care and no vaccine has been licensed (CDC, 2013). However, a clinical trial of a vaccine produced by the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases took place in Uganda in 2009 and showed promise in eliciting an immune response. Further trials are currently underway. BioMARC, a pharmaceutical research center of Colorado State University, was awarded a $2 million contract from the Department of Defense in October 2014 to develop a vaccine to protect against filovirus infection including Marburg Virus and Ebola Virus Disease (Rolston, 2014). The primary goal of the vaccine contract and development is to protect American soldiers from infection with filoviruses—however, it may also be used to stop epidemics in endemic countries.

Chapter 3: Epidemiology and Clinical Picture of Ebola Virus Disease

Ebola Hemorrhagic Fever, now known as Ebola Virus Disease (EVD), is caused by infection with one of five known serotypes of the Ebola Virus. The virus was first isolated in 1976 during an epidemic of an unknown hemorrhagic fever in Zaire (now known as the Democratic Republic of the Congo) and Sudan near the Ebola River. The isolated virus was similar to Marburg virus but antigenically distinct leading to the naming of a new virus (Howard, 2005). The five known serotypes include: *ebolavirus Zaire, ebolavirus Sudan, ebolavirus Tai Forest* (previously known as *ebolavirus Ivory Coast*), *ebolavirus Bundibugyo* and *ebolavirus Reston*. The first four are known to cause disease in humans and nonhuman primates while workers exposed to *ebolavirus Reston* have developed antibodies but no disease (WHO, 2014). The five known serotypes of the Ebola Virus are unique enough that it is thought they may each have their own reservoir, although no reservoirs have been confirmed for any of the serotypes (MacNeil et al, 2011).

Since its discovery, Ebola epidemics have increased in frequency and size due to increases in human population density, resulting in spread into previously uninhabited forested regions and larger populations exposed to the virus. All previous epidemics of EVD have been relatively small in size, isolated to rural villages and contained through isolation of cases and the instillation of strict barrier nursing protocol (Howard, 2005). The ongoing epidemic in West Africa is by far the largest epidemic of Ebola to date, due to the fact that it was the first to hit a major urban center before successful containment measures could be implemented.

Since its discovery in 1976, epidemics have occurred sporadically in Uganda, the Democratic Republic of the Congo (DRC), Gabon, and South Sudan—therefore, the endemic

region of the virus was thought to be limited to tropical rainforests of Central Africa (CDC, 2014). A single 1994 case in an ethnologist infected during an autopsy of a chimpanzee in Cote d'Ivoire widened the potential endemic region to include West Africa and this was further supported by the first case in Guinea in 2013 that started the ongoing epidemic in West Africa. Additionally, samples initially taken for Lassa fever in Sierra Leone tested positive for Ebola upon retesting in 2014 and demonstrate that Ebola virus was in Sierra Leone at least as early as 2006 (Schoepp, 2014). The uncertainty associated with the endemic region of viruses that cause EVD stems from the failure to confirm the reservoir of the virus. Initial epidemics implicated primates as the reservoir, but current research points to fruit bats of the Pteropodidae family as the natural reservoir (WHO, 2014). Transmission to humans occurs through a spillover event where humans come in direct contact with the blood or other bodily fluids of an infected nonhuman primate or bat. This most often occurs when hunters kill an infected animal and become infected during the slaughtering process or through the consumption of undercooked contaminated bush meat. After the spillover event, human-to-human transmission occurs through direct contact with contaminated body fluids including: blood, sweat, semen, vomit, saliva, urine, feces, tears and breast milk and/or contact with materials contaminated with these fluids (WHO, 2014). Therefore, most secondary cases occur in healthcare workers and close family members or funerary workers who come in contact with the body. It is important to note that semen has been found to be infectious in recovered patients for up to 7 weeks and that dead bodies are contagious for as long as the virus remains in body fluids (WHO, 2014). It is not known whether EVD can be passed from a recovered patient to a sexual partner, and thus abstaining from sex or condom use is strongly recommended in the first three months following infection (CDC, 2014).

The incubation period of EVD is 2-21 days with an average incubation period of 8-10 days (CDC, 2014). The clinical picture of the disease is indistinguishable from Marburg Virus Disease and initial symptoms include: headache, fever, muscle pain, fatigue and sore throat. Humans are not infectious and cannot therefore transmit EVD to other humans until they show symptoms of the disease (CDC, 2014). Following the initial symptoms, patients develop vomiting, diarrhea, rash, and abdominal pain. Some patients will also develop internal and/or external hemorrhaging. Recent clinical data suggest that most patients also experience low white blood cell and platelet counts along with an elevation in liver enzymes (WHO, 2014). The clinical symptoms of EVD are difficult to distinguish from several other diseases that are endemic to the region including: Malaria, Typhoid Fever and Meningitis. In order to confirm diagnosis with one of the four serotypes that cause EVD in humans, one of the following laboratory tests must be conducted: ELISA, antigen-capture detection, serum neutralization, RT-PCR assay, electron microscopy or cell culture. Due to biohazard risks, all laboratory tests of active samples should be conducted under Level 4 biosafety conditions (WHO, 2014).

The case fatality rates of previous epidemics range from 25-90%, averaging around 50% (WHO, 2014). There is no clinically proven treatment method, however, treatment methods currently being used include: supportive care, plasma transfusions from recovered patients, along with several potential antiviral drugs such as ZMapp, TKM-Ebola, Favipiravir and Brincidofovir (Leonard, 2014). The ongoing epidemic in West Africa has sped up previous research into therapeutic and preventative vaccines that had stalled due to lack of funds and pharmaceutical interest in the development of a vaccine for a virus with such a low annual incidence rate. Three different vaccines are currently undergoing trials in the United States and the United Kingdom: 1) cAd3-ZEBOV by GlaxoSmithKline in collaboration with the US National Institute of Allergy

and Infectious Diseases, 2) rVSV-ZEBOV developed by the Public Health Agency of Canada and licensed to NewLink Genetics and 3) Ad26-ZEBOV + multivalent MVA-ebola virus by Johnson & Johnson with AdVac technology from Crucell Holland and MVA-BN technology from Bavarian Nordic (WHO, 2014; ECDC, 2015). The effectiveness of the treatment methods described above and further information on the vaccines currently in clinical trial will be further discussed in subsequent chapters.

The current Ebola epidemic has vastly increased scientific knowledge of EVD, especially as related to treatment and survival. For example, cases like American doctor Ian Crozier's demonstrated that aggressive life-support measures like ventilators and dialysis could improve survival in some patients (Beaubien, 2014). Additionally, basic supportive care involving monitoring and replacing fluid and electrolyte loss through IVs and control of bleeding disorders has significantly decreased case fatality rates from Ebola virus (WHO, 2014). Most importantly, however, the ongoing Ebola epidemic has demonstrated the need for an immediate and effective response to future hemorrhagic fever epidemics as they become exponentially more difficult to control once they spread through urban centers and poorly equipped medical centers.

Chapter 4: Previous Ebola Virus Disease Epidemics

As stated in the previous chapter, most Ebola Virus epidemics have been relatively small, occurred in rural areas and were controlled through isolation of cases and the strict use of barrier nursing protocols. Epidemics of EVD usually take place during or at the end of the rainy season and all index cases have occurred in people living in or in close proximity to a tropical rainforest (Howard, 2005). Many epidemics have resulted in the infection of healthcare workers and family members who were treating patients or preparing the body for burial before proper infection control protocols were enacted.

Prior to the ongoing epidemic in West Africa, the only known virus to have a greater case fatality rate for humans was Rabies (Howard, 2005). Since cases of EVD are often misdiagnosed as other diseases with similar presentations such as Yellow Fever and Malaria, EVD outbreaks tend to have an extremely high case fatality rate early on that is reduced over time as cases are diagnosed and provided supportive care much earlier in the clinical course of the disease (Howard, 2005). Many researchers believe that previous epidemics of EVD have ended due to the inability of the Ebola virus to transmit through the air and the remoteness of infected bats and monkeys rather than through human efforts to contain them (Howard, 2005; WHO 2014). This chapter details the history of previous epidemics of each Ebola virus serotype.

Ebolavirus Zaire

In August of 1976, an outbreak of an unknown hemorrhagic fever erupted in Northern Zaire (DRC). The first case occurred in a teacher accompanying a group of missionaries from the Sisters of the Holy Heart of Maria located in Yambuku to the North. The teacher fell ill several days into the trip and unknowingly infected several of the missionaries who spread the virus to

dozens of villages through direct contact and the reuse of contaminated syringes (Francis et al, 1976). He was unresponsive to Malaria treatment, began bleeding from multiple sites and died along with several family members whom he passed the virus to (Francis et al, 1976). Doctors working on this outbreak described a disease characterized by fever, vomiting of black blood, pain in the abdomen and chest, bloody stools, bleeding from the nasal orifice and mental confusion (Howard, 2005). Of the 318 documented cases in the Yambuku region epidemic, 280 died resulting in a case fatality rate of 88% and an overall attack rate of 8 per 1,000 population (CDC 2014; Howard, 2005). Early on in the epidemic, a Belgian doctor working in Yambuku sent a blood sample from a Belgian nurse who died of the disease to the Institute of Tropical Medicine in Antwerp (Brown, 2014). Peter Piot, a young doctor and microbiologist, was the first to isolate and photograph the virus that resembled but did not match the Marburg virus. He was sent with a Belgian team to Yambuku to assist in the effort to contain the epidemic and gather further information on the epidemiology and clinical manifestation of the disease. He and his team named the virus Ebola after the closest river to Yambuku on an inaccurate map. After the detection of several additional serotypes, it was named *ebolavirus Zaire* after the country where the virus was first discovered (Brown, 2014).

Over the next 15 years, a few solitary cases of *ebolavirus Zaire* were identified in Central Africa. The mid 1990s, however, saw a significant increase in the frequency and size of Ebola epidemics. A large epidemic occurred in a mining camp in Gabon in 1994 resulting in 52 cases and 31 deaths (60% CFR). Only months later, the World Health Organization was notified of a hemorrhagic fever like illness occurring in Kitwit, Zaire that was confirmed to be *ebolavirus Zaire* (WHO, 2014). The epidemic was traced to a man who worked in the forest directly outside the city. There were 315 documented cases and 250 deaths (81% CFR). With a population of

400,000 people in 1995, this was the first time an Ebola epidemic occurred in close proximity to a city and it spread easily through the urban hospitals and clinics. In 1996, two separate epidemics of the Zaire serotype occurred in Gabon—one with 37 cases and 21 deaths (57% CFR) and the other with 60 cases and 45 deaths (75% CFR). An additional case linked to the Gabon epidemic involved the infection of a healthcare worker involved in the treatment of EVD patients developing disease in a South African hospital and infecting a local nurse who died of the disease (CDC, 2014). Since the early 2000s, large epidemics of this serotype have occurred in DRC every couple of years. The ongoing epidemic in West Africa and the separate epidemic in the DRC that was declared over in November 2014 are of the Zaire serotype. For further data on *ebolavirus Zaire* epidemics, refer to Table 1, which includes information all confirmed EVD epidemics.

Ebolavirus Sudan

In June of 1976, two months before the epidemic of a hemorrhagic fever in neighboring DRC that resulted in the isolation and identification of a new virus named Ebola, a similar epidemic of hemorrhagic fever occurred in what is now South Sudan. A man who worked at a cotton factory in Nzara, South Sudan became ill and died in a local hospital after experiencing symptoms of fever, hemorrhage and stomach pain (Francis et al, 1976). Several other employees who worked with him became ill and died along with his wife who cared for him while he was sick. The disease spread to the nearby town of Maridi and by the time the epidemic was controlled, 284 people had become ill and 151 people died (53% CFR).

Following isolation of the causative agent, the newly identified serotype of *ebolavirus* was named *ebolavirus Sudan* and the Ebola virus previously identified in the Democratic Republic of the Congo (DRC) became known as *ebolavirus Zaire*. Three years later, a second

epidemic occurred in Nzara and Maridi with 34 cases and 22 deaths (65% CFR). Between 2000 and 2001, an epidemic of the Sudan serotype took place in the Ugandan districts of Gulu, Masindi and Mbarara that resulted in 425 cases and 224 deaths (53% CFR). Another small epidemic occurred in South Sudan in 2004 and Uganda experienced three additional epidemics of this strain between 2011 and 2013 (CDC, 2014).

Ebolavirus Tai Forest

In 1994, an epidemic of hemorrhagic fever occurred among western chimpanzees in the Tai National Forest of Cote d'Ivoire. A week after conducting autopsies on the dead chimpanzees, a Swiss scientist developed symptoms consistent with Yellow Fever and was evacuated to Switzerland for treatment. She, along with the majority of the dead chimpanzees, tested positive for Ebola with a serotype distinct enough from the Sudan and Zaire strains to be given its own name. It was originally named *ebolavirus Cote d'Ivoire* but was officially changed to ebolavirus Tai Forest in 2010 (WHO, 2014). This is the only confirmed case of this serotype causing human infection and since the scientist survived after receiving supportive care it has a CFR of 0%.

Ebolavirus Reston

In an animal research facility in Reston, Virginia an epidemic of a hemorrhagic fever like illness erupted in November of 1989 among Crab-eating Macaques that had been imported from the Philippines. After several animals died from the mysterious illness, the research facility sent blood samples to the nearby US Army Medical Research Institute of Infectious Diseases (USAMRIID) where a new serotype of the Ebola Virus was identified and named *ebolavirus Reston* (CDC, 2014). A major containment effort was launched due to the known mortality rate of Ebola Viruses and the animal research center's proximity to Washington DC. The remaining

animals were killed, the entire facility was decontaminated and all employees who had contact with the macaques were put under observation. No staff members became ill, however, several of them developed antibodies to the virus (Howard, 2005). The discovery of *ebolavirus Reston* was important in that it suggested the possibility that there were serotypes of *ebolavirus* outside of the African continent and that at least the Reston serotype could cause subclinical infection. Since the discovery of the Reston serotype, several epidemics have occurred in nonhuman primates that resulted in seroconversion but no disease in humans who worked with the infected animals (WHO, 2014). In 2008, an epidemic of *ebolavirus Reston* occurred on a pig farm in the Philippines—this was the first reported case of an Ebolavirus infecting and causing disease in pigs (CDC, 2014). The Reston serotype of the Ebola virus has only been found in the Philippines, but could be endemic in other areas.

Ebolavirus Bundibugyo

In August of 2007, a hemorrhagic fever epidemic began in Bundibugyo district of Uganda. Several months passed before samples were sent to the CDC in Atlanta where a new serotype of the Ebola Virus was isolated and named after the district where the epidemic was taking place (MacNeil et al, 2011). An epidemic response team consisting of national and international partners implemented effective control measures and managed to contain the epidemic after a few weeks in the field. There were 149 cases and 37 deaths (CFR 25%). A second epidemic of serotype Bundibugyo took place in DRC in 2012 with 36 confirmed cases and 13 deaths (36% CFR). Estimates including probable cases are closer to 80 cases with 36 deaths (CFR 45%). To date, no further epidemics of *ebolavirus Bundibugyo* have been reported (CDC, 2014).

Table 1: Chronology of *ebolavirus* Epidemics—assembled from WHO and CDC data

(http://www.who.int/mediacentre/factsheets/fs103/en/ and http://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html)

Year	Country	Serotype	Case Count	Deaths	CFR
August-November 2014	DRC	Zaire	66	49	74%
March 2014-Present	Multiple[1]	Zaire	23729	9604	41%
November 2012-January 2013	Uganda	Sudan	6*	3	50%
June-November 2012	DRC	Bundibugyo	57	29	51%
June-October 2012	Uganda	Sudan	11*	4	36%
May 2011	Uganda	Sudan	1	1	100%
December 2008-February 2009	DRC	Zaire	32	15	47%
November 2008	Phillipines	Reston	6[2]	0	0%
December 2007-January 2008	Uganda	Bundibugyo	149	37	25%
2007	DRC	Zaire	264	187	71%
2004	Russia	Zaire	1[3]	1	100%
2004	South Sudan	Sudan	17	7	41%

November-December 2003	**DRC**	**Zaire**	**35**	**29**	**83%**
December 2002-April 2003	**DRC**	**Zaire**	**143**	**128**	**89%**
October 2001-March 2002	**Gabon**	**Zaire**	**65**	**53**	**82%**
2000-2001	**Uganda**	**Sudan**	**425**	**224**	**53%**
1996	**Russia**	**Zaire**	**1**[3]	**1**	**100%**
1996	**Philippines**	**Reston**	**0**	**0**	
1996	**USA**	**Reston**	**0**	**0**	
1996	**South Africa**	**Zaire**	**2**[4]	**1**	**50%**
July 1996-January 1997	**Gabon**	**Zaire**	**60**	**45**	**75%**
January-April 1996	**Gabon**	**Zaire**	**37**	**21**	**57%**
1995	**DRC**	**Zaire**	**315**	**250**	**81%**
1994	**Cote d'Ivoire**	**Tai Forest**	**1**	**0**	**0%**
1994	**Gabon**	**Zaire**	**52**	**31**	**60%**
1992	**Italy**	**Reston**	**0**	**0**	
1989-1990	**Philippines**	**Reston**	**3**[2]	**0**	**0%**
1990	**USA**	**Reston**	**4**[2]	**0**	**0%**

1989	**USA**	**Reston**	**0**	**0**	
1979	**South Sudan**	**Sudan**	**34**	**22**	**65%**
1977	**DRC**	**Zaire**	**1**	**1**	**100%**
1976	**England**	**Sudan**	**1**[3]	**0**	**0%**
1976	**South Sudan**	**Sudan**	**284**	**151**	**53%**
1976	**DRC**	**Zaire**	**318**	**280**	**88%**

*refers to confirmed cases only—total cases likely higher

[1] majority of the epidemic in Guinea, Sierra Leone and Liberia with imported cases in Mali, the US, Nigeria, Senegal, Spain and the UK—case count is accurate as of …

[2] refers to number of people who developed antibodies but did not have symptoms of disease

[3] refers to a case(s) resulting from contamination in a laboratory setting

[4] first case imported from epidemic in Gabon and secondary case in a healthcare worker who treated the patient

Chapter 5: The Ongoing Ebola Virus Disease Epidemic in West Africa

In early December 2013, a 2-year-old boy named Emile Ouamouno developed fever, headache and bloody diarrhea in a small village named Meliandou—located in Southern Guinea (Baize et al, 2014). Despite receiving care from his family, he died on December 6th. Within weeks, the boy's father was the only survivor in the household after his grandmother, sister, mother and her unborn child all died of a similar disease (Stylianou, 2014). Due to the remoteness of Meliandou, the endemicity of multiple diseases with similar symptoms in this region, and the fact that no health workers in Guinea had ever seen a case of EVD before, the first cases of what is now the largest Ebola Virus Disease epidemic in history did not draw much attention (WHO, 2014). As a result, community health workers who treated the first EVD cases did not use infection control measures, became infected and spread the virus to nearby villages and district hospitals where the disease spread quickly without proper infection control measures. An investigative team led by the WHO to trace the source of the epidemic suggested that 4 out of the first 15 deaths (27%) attributed to this epidemic were among healthcare workers (Baize et al, 2014). Three months passed before the Ministry of Health in Guinea was notified of a large epidemic of an unknown hemorrhagic fever occurring in the Southern Region (WHO, 2014). The WHO was notified several days later and declared it an EVD epidemic on March 25th. Days later the first cases were confirmed in neighboring Liberia. On May 26th, the first cases were confirmed in Sierra Leone and importation eventually occurred to nearby Mali, Nigeria, and Senegal and eventually to the United States, the United Kingdom and Spain. However, Guinea, Liberia and Sierra Leone remained the focal point of the epidemic and transmission was ongoing (WHO, 2014).

The WHO team along with a second team sent on behalf of Guinea's Ministry of Agriculture and Forestry traced the epidemic back to the village of Meliandou and conducted interviews with villagers in an attempt to determine the way zoonotic transmission had occurred (Saez et al, 2014; Baize et al 2014). There are two routes through which the Ebola virus is thought to cause infection in humans: 1) an EVD epidemic among non-human primates where a human comes in direct contact with the bodily fluids of one of those infected animals, and 2) a reservoir such as a fruit bat which sheds the virus in its body fluids but does not show symptoms of disease comes in contact with a human through hunting or some other activity (CDC, 2014). After an extensive investigation of the surrounding areas, the team determined that the first mode of transmission was unlikely since it had previously been characterized by a significant decline in large wildlife populations during EVD epidemics and such a decline had not occurred (Walsh et al, 2003; Baize et al, 2014). Therefore, it is likely that the infection was the result of direct or indirect contact with an infected bat(s) (Saez et al, 2014). This has been demonstrated to occur through hunting, consumption of undercooked contaminated bat meat and close proximity to bats carrying the virus that results in contact with contaminated feces (CDC, 2014). Due to the fact that there were no bat hunters in the household and none of the family had reported eating bat meat prior to the epidemic, it is likely the child developed EVD from contact with contaminated droppings or direct contact with an infected bat—not from contaminated bushmeat as has often been reported. It is also possible that the child became ill from contact with a person experiencing subclinical or mild infection, however, researchers did not directly explore this possibility and at the time of investigation little was known regarding subclinical and mild EVD infections. It is important to note, that most theories involving the likely reservoir of EVD have involved certain species of the fruit bat and villagers reported that these bats were not very

common in the region and there were no large colonies nearby (Baize et al, 2014). However, the villagers did report large colonies of insect-eating free-tailed bats and that the little boy who represents the first known case of the epidemic had lived 50 meters from a tree containing a large colony. The villagers explained that the local children often played in the tree and attempted to hunt the bats for food (Baize et al, 2014). The tree had burned down since, but the team confirmed the presence of *Mops condylurus* (a species of insect-eating bats) through soil samples. A study conducted in 2009 had suggested serological evidence of Ebola Virus exposure in this species (Pourrut et al, 2009). Therefore, the team concluded that there were two likely sources of infection for the index case: contact with a live and/or contact with contaminated feces of an infected fruit bat or an insect-eating bat. The team collected more than a hundred specimens of several different species in the area but none of them tested positive for the Ebola virus and their antibody tests were inconclusive (Saez et al, 2014). The team still concluded, however, that the evidence suggests a single zoonotic transmission event likely caused by contact with an infected insect-eating bat since fruit bats are much less common in the region—and was followed by sustained human-to-human transmission (Saez et al, 2014; Baize et al, 2014; WHO 2014).

As of 2 March 2015, WHO records indicate that there have been 23,913 cases (14,314 of which are laboratory-confirmed) and 9,714 deaths (CFR 41%). The estimated number of cases that arise from a single case (called R0) ranges from1.5 to 2.2 in this epidemic (*Ebola in Graphics*, 2015). Although the case data are very incomplete, WHO has disaggregated case data by age and sex for each country (cases were included if at least one of these factors were known). However, the data does not include information on which cases survived and so the question of whether differential survival rates exist for the virus is ongoing. The WHO data

suggests that infection rates in males and females are similar in all three countries (WHO, 2015). However, as with previous epidemics of hemorrhagic fevers and EVD epidemics specifically, the disease is worse in pregnant women. Only a few pregnant women have been known to survive EVD infection, and until very recently, not a single one had managed to carry their child to term. Viruses associated with hemorrhagic fevers tend to attack the fetus and cause spontaneous abortion; this is compounded by the severe illness of the mother and the risks this poses for the fetus. There are several theories about why EVD is so fatal to a pregnant woman and even more so to her unborn child. One of these theories suggests it is possible that the virus accumulates in the womb. An MSF doctor working in West Africa conducting informal research claims to have measured the highest viral load she had ever seen in the blood and fluids of the afterbirth from a spontaneous abortion caused by Ebola (Sieff, 2015).

Although gender does not appear to have an effect on the attack rate of the virus, age does appear to be an important factor in determining risk of infection. Even though children aged 0-14 years old comprise 43% of the population in these three countries, they only account for 20% of all Ebola cases (WHO, 2015). People aged 15-44 years old appear to be 3 times more likely to develop infection than children 0-14 years old, and people aged 45 years old and older appear to be 4 times more likely to develop infection than children 0-14 years old (WHO, 2015). Known infections in healthcare workers account for 816 of confirmed cases in Guinea, Liberia and Sierra Leone combined and is a significant risk factor for developing disease (WHO, 2015). A study conducted by MSF in the Ebola Management Center of Kailahun, Sierra Leone showed that health workers also had a 52% higher CFR ($p=0.05$) from the disease and suggested that further research was necessary to determine the cause (Dallatomasinas et al, 2014). Please refer to Figure 1 at the end of this chapter for a timeline of the West African epidemic.

Guinea

Guinea has a total population of 11.75 million people and 10 doctors per 100,000 people (*Ebola in Graphics*, 2015). This is devastatingly low compared to the 245.2 doctors per 100,000 people in the United States. It is, however, over five times higher than the number of doctors per 100,000 people in Sierra Leone and Liberia (*Ebola in Graphics*, 2015). As of March 2nd 2015, the total EVD case count in Guinea was 3205, of which 2808 were laboratory confirmed (CDC, 2015). The total deaths were 2127 (CFR 76% among laboratory confirmed cases, CFR 66% if suspected cases are included). Guinea's weekly case counts did not leap exponentially to the same extent as Liberia or Sierra Leone—it is possible that this is due to the comparatively higher number of doctors per 100,000 people or to marginally better linkages to care. The highest number of new cases reported per week never exceeded 200, whereas this number reached as high as 500 in Liberia and 650 in Sierra Leone (WHO, 2015). In mid-December, the epidemiologic curve for Ebola started to a show a significant downward trend and only a few new cases were reported each week. However, weekly case reports leading up to March 2nd 2015, showed a slight increase in cases with approximately 30 reported each week, some in a prefecture with no previous reported cases in this epidemic (WHO, 2015). Guinea has experienced many apparent weeks of control only to see spikes in new cases in the following weeks. This is thought to be the result of reintroductions of the virus across Sierra Leone's porous borders between Liberia and Sierra Leone and indicates that control of the virus in Guinea is dependent upon control in it's neighboring countries (WHO, 2014).

Liberia

Liberia has a total population of 4.294 million people and only 1.5 doctors per 100,000 people (*Ebola in Graphics*, 2015). As of 2 March 2015, the total EVD case count in Liberia was 9265, of which 3153 were laboratory confirmed. The total deaths were 4057—CFR 78% among laboratory confirmed cases, CFR 44% if suspected cases are included (CDC, 2015). The first confirmed cases of EVD in Liberia were announced on March 31st 2014 and within a month there were 34 cases and 6 deaths from the disease. The first Ebola cases were reported in the capital of Monrovia in mid-June and within two weeks most schools, border crossings and many hospitals were closed as EVD spread quickly through the densely populated city with low access to health care and sanitation (WHO, 2015). Hospitals and clinics closed as a result of staff shortages and inadequate resources to treat Ebola cases. In addition, due to the inadequacy of health facilities to house the growing number of Ebola patients at the beginning of the epidemic in Liberia and widespread fear of the disease, many patients did not seek care or were turned away from health facilities when their symptoms suggested EVD (WHO, 2015). By the beginning of August, the epidemic peaked with around 500 new cases occurring in the country per week for over two months. In late September, a 150-bed treatment facility was built in Monrovia that increased the total beds for Ebola victims in the city to 240. Within 24 hours, the unit was full and patients lined up outside (*Ebola Virus Disease in West Africa,* 2014). Weeks later, however, the epidemic curve started to show a downward trend. It spiked again in November 2014 and has steadily declined since. In the week leading up to March 2nd 2015, only one new case of Ebola was reported in Liberia and several districts have reported no new cases for several weeks (WHO, 2015).

Sierra Leone

Sierra Leone has a total population of 6.092 million people and just over 2 doctors per 100,000 people. As of 2 March 2015, the total EVD case count in Sierra Leone was 11443, of which 8353 were laboratory confirmed. The total deaths were 3530—CFR 42% among laboratory confirmed cases, CFR 31% if suspected cases are included (CDC, 2015). The first confirmed cases of EVD in Sierra Leone were announced on 26 May 2014. They appear to have resulted from the infection of a traditional healer who had been working to treat Ebola victims in Guinea (WHO, 2015). At her funeral, the body was washed by local women and touched and kissed by family members, as is traditional practice in the region. Fourteen cases were directly traced to this funeral and the virus spread quickly through the region. Hospitals and clinics were quickly overwhelmed. Sierra Leone's rainy season from June to August seriously disrupted treatment as patients had further difficulty accessing care. A major blow came when the country's only hemorrhagic fever expert died from Ebola in Kenema during this time (WHO, 2015). By early September the number of new cases per week increased drastically to 400. In late September 2014, the WHO estimated that Sierra Leone was 532 beds short of being able to handle the growing epidemic. By November, the patient database showed almost 700 incident EVD cases per week compared to WHO laboratory-conformed cases per week of 540 ((*Ebola in Graphics*, 2015) At this point, significant efforts to increase bed capacity and healthcare personnel by Cuba, the UK and the US started to slow the epidemic (WHO, 2015). As the country with the largest number of cases, however, the epidemic in Sierra Leone has been more difficult to bring to a close. In many districts, the Government of Sierra Leone was forced to resort to lock-down measures with residents unable to leave their homes for days at a time while health teams searched for cases, bodies and distributed sanitation products such as soap. Such

measures reported major success and case counts have gone down drastically, yet still slower than in neighboring Liberia and Guinea. In the week leading up to 2 March 2015, sixty-four new cases of EVD were reported in Sierra Leone of the ninety-nine total new cases reported for the region (WHO, 2015).

Nigeria

The first case of EVD arrived in Nigeria by plane from Liberia on 20 July 2014. The patient had symptoms of Ebola and threw up several times on the plane. After being hospitalized on arrival, he infected several healthcare staff who did not recognize his symptoms as Ebola and therefore did not use personal protective equipment or follow appropriate protocols. A patient in the hospital was also infected after being treated by the same healthcare workers (WHO, 2014). The imported EVD case died several days later and ultimately infected 19 Nigerians. None of the passengers on the plane became infected with the virus. Of the 20 cases in Nigeria, 8 died (CFR 40%). Nigeria presents clear evidence that when Ebola is identified quickly, and contact tracing is immediately implemented, virus transmission can be stopped well before it reaches epidemic levels (WHO, 2014). It is important to note, however, that Nigeria had a large team of people trained by CDC to conduct contact investigations for Polio as well as a command center funded by the Bill and Melinda Gates Foundation. Their skills and resources were redirected towards the Ebola response in Nigeria and further transmission of the virus was prevented. Nigeria was declared Ebola free on 20 October 2014, after 42 consecutive days with no new Ebola cases (represents two complete cycles of the longest known incubation period). Control of the Ebola importation into Nigeria was a critical moment in the Ebola response because Nigeria has a population of 173.6 million people and failure to contain the spread of the virus within this country could have resulted in major growth of the epidemic (WHO, 2014).

Mali

On 23 October 2014, the first confirmed case of EVD was reported in Mali in a 2-year old girl who had been brought from Guinea by her extended family when the rest of her family passed away from Ebola (WHO, 2015). The child died several days later; though over 100 people had direct contact with the patient and were traced, no further cases developed. On 12 November 2014, a separate confirmed epidemic of the virus was reported in the capital, Bamako. A religious leader from Guinea developed symptoms of the disease and passed the virus to the nurse who cared for him. Intense contact tracing was conducted and a total of 8 cases developed from contact with the Imam (he was counted as a Guinean case). Of the 8 Malian cases, 6 patients died (CFR 75%). On 18 January 2015, Mali was declared Ebola free after no new Ebola cases were reported for 42 days (WHO, 2015).

Senegal

The first confirmed case of Ebola in Senegal was reported on 29 August 2014, in a man who had traveled from Guinea to the capital of Senegal, Dakar. Senegal immediately enacted their Ebola response protocol and maintained careful supervision of all detected contacts. The man who imported the virus to Senegal recovered and returned to Guinea. No further cases developed and Senegal was declared Ebola on 17 October 2014 after 42 days with no new cases (WHO, 2014).

United States

As of 2 March 2015, there were 10 cases of Ebola in the United States. Of these, 6 were medical professionals who contracted and tested positive for the virus while working to combat the epidemic in West Africa and were evacuated to the US for treatment. Two additional health care workers developed symptoms and were diagnosed after returning from working on the

response in West Africa. The further US cases were the direct result of improper use of personal protective equipment during the treatment of one patient diagnosed and treated in a Texas hospital after he was exposed to the virus in Liberia and came to the United States to see his family (CDC, 2014). No further cases developed. Only 4 of the 10 patients treated in the US are considered US cases due to the fact that cases are counted in the country where the individual became infected. Of the 4 cases that developed symptoms and were diagnosed in the US, there was 1 death (CFR 25%).

On 25 September 2014, the Liberian national mentioned above developed symptoms of fever, abdominal pain, dizziness, nausea and headache; he sought care at Texas Health Presbyterian Hospital in Dallas. Reports conflict over whether his travel history was discussed. The family of the patient, Thomas Duncan, claims that he mentioned a recent history of travel to West Africa to his nurse who did not pass the information along to his doctors who prescribed antibiotics and sent him home (Fernandez and Sack, 2014). The hospital claims that he did not mention his recent travel history and that he was not asked because it was not part of their standard triage protocol at that time. By 28 September 2014, Thomas's health deteriorated further and an ambulance took him back to Texas Health Presbyterian Hospital (CDC, 2014). This time the patient's history of travel was assessed immediately and the doctor ordered an Ebola test to be conducted and began following CDC protocol. The CDC was called in the afternoon and Thomas was moved to an Intensive Care Unit that had been evacuated of all other patients. On 30 September 2014, his Ebola test came back positive and his condition continued to deteriorate with short periods of apparent improvement (CDC, 2014). The hospital contacted Chimerix, the company producing the drug Brincidofovir, which was being developed to potentially treat EVD and requested a dose. The hospital received the drug on 4 October and

began administering it immediately. After some initial improvement in Thomas's condition, he passed away on 8 October 2014 (CDC, 2014). He became the first patient to die of EVD in the US. If he had survived, the Liberian government had considered pressing charges against him because he had signed a document at the airport claiming he had no contact with anyone who had symptoms of EVD. Thomas claimed before he passed away that he had thought the woman he had helped transport to the hospital in Monrovia, Liberia was having a miscarriage and that he had no idea he had been exposed to Ebola (WHO, 2014).

Everyone who had had contact with Thomas Duncan was asked to stay home and monitor his or her temperature for 21 days. On 10 October 2014, Nina Pham, a nurse who had been part of the healthcare team treating Thomas Duncan, developed a fever and was placed in isolation. She tested positive for the virus and was transferred to the National Institutes of Health Clinical Center in Bethesda, Maryland due to fear that Texas Health Presbyterian Hospital was not following proper infection control protocol and this had led to Nina Pham contracting the virus while caring for Thomas Duncan. Nina recovered quickly and was declared virus free and discharged on 24 October (CDC, 2014).

On 14 October 2014, Amber Vinson, a second nurse on the team that had treated Thomas Duncan, developed a fever while visiting her family in Ohio. She was given permission to fly back to Dallas by CDC staff that later said she should not have flown (her fever was below the cutoff for a true fever so she was not deemed a high risk flyer. The CDC later changed the regulations to prevent people being monitored for exposure to the virus from traveling. Amber Vinson tested positive for Ebola and was transferred to Emory University Hospital in Atlanta (Davidson, 2014). She was treated and discharged on 21 October 2014. Dozens of people who

had contact with Amber were traced and their temperatures monitored for 21 days—no further cases developed from her or from the remaining contacts of Thomas Duncan (CDC, 2014).

On 23 October 2014, an American doctor named Craig Spencer who had been working in Guinea tested positive for Ebola at Bellevue Hospital Center in New York City. He responded to treatment and was discharged on 7 November. No further cases developed among his personal contacts or among the health staff that participated in his treatment (CDC, 2014). These are the four patients considered US cases of EVD—of the four, only Thomas Duncan died (CFR 25%).

As of 2 March 2015, six additional American citizens have been evacuated from West Africa and treated for Ebola in the United States. Doctor Kent Brantly and missionary Nancy Writebol were airlifted to Emory University Hospital in Atlanta, GA from Liberia in early August after testing positive for the virus in West Africa (CDC, 2014). Both were treated with an experimental drug called ZMapp and received plasma transfusions from people who had recuperated from the virus. They recovered and were discharged on 21 August 2014 (WHO, 2014).

American doctor Rick Sacra tested positive for Ebola in Liberia and was airlifted to the Nebraska Medical Center in Omaha. He was treated with an experimental drug called TKM-Ebola and received a plasma transfusion. He was declared Ebola free and discharged on 25 September 2014.

American doctor Ian Crozier tested positive for Ebola in September after working in an overwhelmed isolation ward in Kenema, Sierra Leone. He was airlifted to Emory University Hospital in Atlanta and became the sickest Ebola patient to be treated by Emory Hospital (Grady, 2014). He deteriorated quickly, went into multiple organ failure as a combined result of Ebola and a severe case of viral Hepatitis. He was given a transfusion of plasma from an Ebola survivor

but his condition continued to deteriorate. The staff and his family did not think he would recover and that if he did he would suffer permanent brain damage (Beaubien, 2014). However, he suddenly started to produce antibodies and his viral load began to fall. He recovered slowly and was discharged Ebola free on 19 October 2014. He says that his brain seems to work slower than before he was ill but hopes to make a full recovery and return to treat further Ebola patients in West Africa (Grady, 2014).

American photojournalist Ashoka Mukpo tested positive for the virus while covering the Ebola epidemic in Liberia. He was airlifted to the Nebraska Medical Center in Omaha on 6 October 2014 where he received a plasma transfusion and an experimental drug called Brincidofovir. He recovered and was discharged on 22 October 2014 (CDC, 2014).

Doctor Martin Salia, a citizen of Sierra Leone and married to an American, tested positive for Ebola while working in Sierra Leone. His first test after exhibiting symptoms was negative and this delay may have affected his recovery. He was airlifted to the Nebraska Medical Center on 15 November 2014, where he received a plasma transfusion and the experimental drug ZMapp (Soergel, 2014). His condition was poor on arrival as he was already in kidney failure and experiencing acute respiratory distress. He passed away on 17 November 2014.

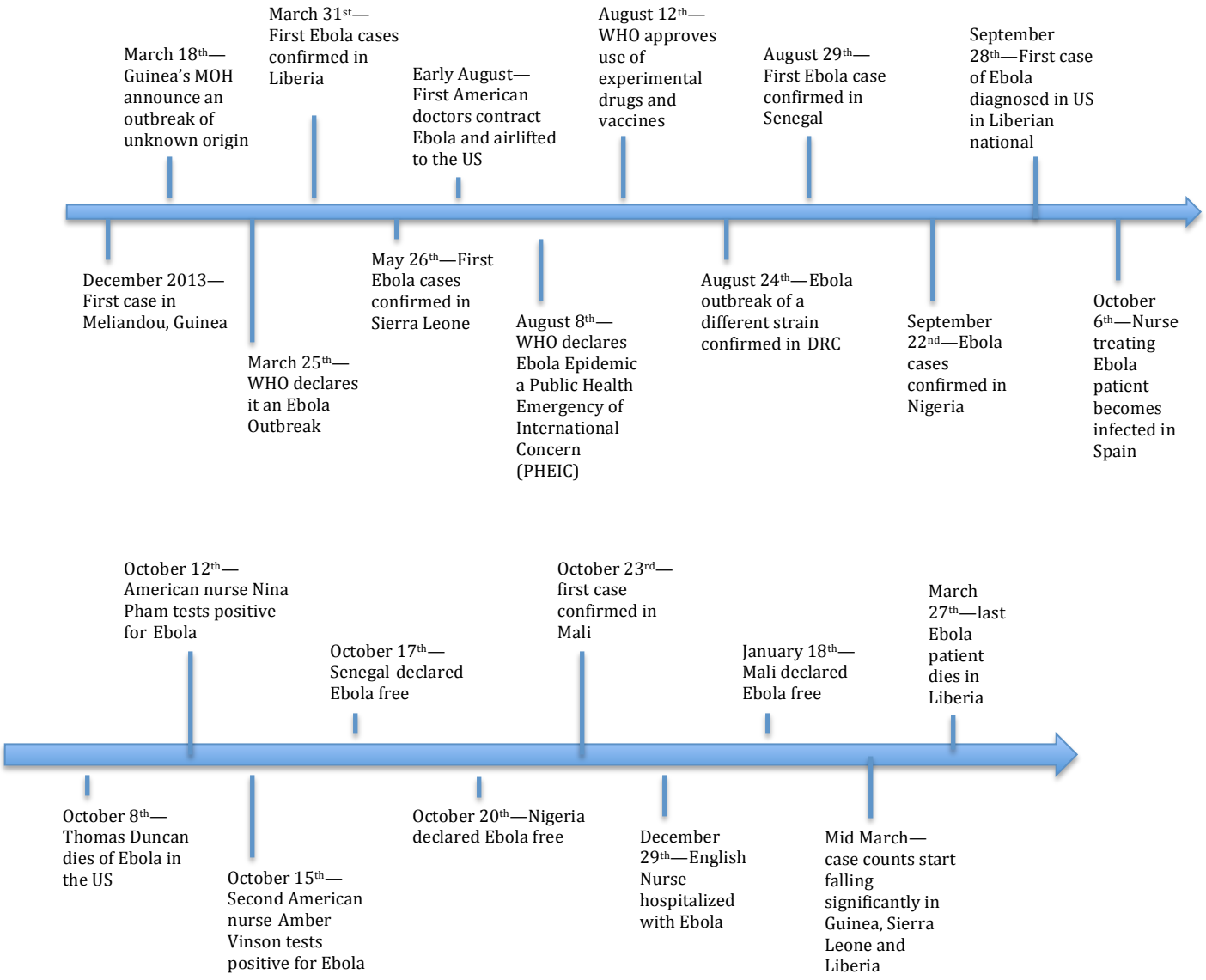
United Kingdom

On 29 December 2014, a Scottish nurse developed symptoms of Ebola after her return from work in Sierra Leone. She recovered and was discharged from an English hospital on 24 January 2015. No further cases developed (Cooper, 2015).

Spain

In August and September 2014, two Spanish priests working in West Africa tested positive for Ebola and were evacuated to a hospital in Madrid. Neither recovered from the virus and both cases were counted in the country where the disease was contracted. On 6 October 2014, a nurse who had been involved in the treatment of one of the priests who had died on 25 September tested positive for Ebola virus and was isolated. Due to the clear breakdown in infection control practices, dozens of other health workers and their contacts were isolated. No further cases developed. The nurse recovered and was discharged on 1 November 2014. Spain was declared Ebola free on 2 December 2014, after 42 days with no reported Ebola cases (WHO, 2014).

Figure 1: A Timeline of the West African Epidemic



Chapter 6: Control & Prevention Measures

Prevention

In order to discuss prevention and control methods, it is necessary to go over the reservoir and transmission of the virus again. Initial epidemics implicated primates as the reservoir, but current research points to fruit bats of the Pteropodidae family as the natural reservoir (WHO, 2014). Transmission to humans occurs through a spillover event where humans come in direct contact with the blood or other bodily fluids of an infected nonhuman primate or bat. This most often occurs when hunters kill an infected animal and become infected during the slaughtering process or through the consumption of undercooked contaminated bush meat. After the spillover event, human-to-human transmission occurs through direct contact with contaminated body fluids including: blood, sweat, semen, vomit, saliva, urine, feces, tears and breast milk and/or contact with materials contaminated with these fluids (WHO, 2014). Therefore, most secondary cases occur in healthcare workers and close family members or funerary workers who come in contact with the body. For further information regarding the reservoir and transmission of the virus please refer back to Chapter 3.

The primary goal of prevention is to prevent the initial zoonotic transmission event that leads to Ebola infection in humans and is further spread by human-to-human transmission. Prevention measures at this initial stage, however, are hampered by several factors: 1) the uncertainty regarding the animal reservoir(s), 2) deforestation and population growth that pushes humans into increased contact with animals potentially infected with the virus, 3) popularity of hunting bats and other potential reservoirs for food consumption in Central and West Africa

where the virus is endemic and 4) the current unavailability of a preventative vaccine against Ebola.

Ideally, countries where the Ebola virus is endemic would ban hunting and consumption of bushmeat in order to prevent as many future zoonotic transmission events as possible. Since the reservoir has not been verified however, and there are many non-human primates that can be infected with the virus and pass it on to humans, this would mean that most bushmeat contact would have to be banned in these countries. This would be very controversial since the role of bushmeat in transmission has not been proven outright. Additionally, a study commissioned by the Food and Agriculture Organization (FAO) explains that in much of rural Africa consumption of bushmeat "represents a vital dietary item for a complex combination of reasons dictated by lack of alternate sources, financial limitations, preference and cultural values. For such people, wild animals constitute a valuable food resource which cannot be easily withdrawn or replaced without causing wide-ranging socio-economic imbalances" (Ntiamoa-Baidu, 1997). In other words, permanently banning the hunting and consumption of bushmeat as a strategy to prevent relatively rare zoonotic transmission events of the Ebola virus would have devastating consequences on the nutritional and economic status of these populations. Further, such practices were unlikely to have been banned in West Africa before 2013 since the Ebola virus was not known to be endemic there and thus would not have prevented the ongoing epidemic in West Africa from occurring. During previous Ebola epidemics, some governments in the affected countries did place temporary bans on the consumption of bushmeat. However, such measures only have the ability to prevent a second zoonotic transmission event (in other words contact between another infected animal that results in human infection unrelated to the previous transmission event). They cannot prevent further human-to-human transmission in an ongoing

epidemic. Since the discovery of the Ebola virus, many scientists have suggested that changes in land use practices in areas bordering forests combined with the dramatic increase in human population over the last 100 years has increased contact with remote wildlife, often increasing exposure to foreign pathogens resulting in the emergence and increasing frequency of epidemics of Ebola and other novel viruses (Morvan et al., 2000). However, this is probably the most difficult avenue for preventative measures, as it would require systematic political, economic and social policies.

A preventative vaccine could protect high-risk groups such as health workers and hunters from contracting the virus, but it would be difficult to determine who should receive the vaccine and how best to conduct a vaccination program to reach the rural populations that would most benefit from it. This prevention method is also reliant on the heretofore unsuccessful production of a safe and efficacious vaccine. To sum, primary preventative measures to stop the initial zoonotic transmission event are challenging and likely to be ineffective.

The next level of prevention focuses on educational activities that occur prior to the zoonotic transmission event. These secondary preventative measures include: 1) educating communities about how Ebola virus can be spread from one person to another, 2) encouraging hand washing, 3) educating all healthcare workers about proper infection control practices, and 4) training healthcare workers to suspect Ebola infection and to take/send blood samples for testing. As with primary prevention strategies, secondary prevention strategies are challenging and require large financial and personnel resources to effect behavior change in rural communities on the fringe of forests where Ebola epidemics typically first occur (Wilcox, 2006).

Preventative measures at the individual level for people in countries with an ongoing Ebola epidemic include: 1) practice careful hygiene (e.g. hand washing, using hand sanitizer, and

avoiding contact with the body fluids of others), 2) do not handle items that may have come in contact with the body fluids of infected individuals (e.g. linens, needles, and medical equipment), 3) avoid burial rituals that involve handling the body or items of an individual who died from Ebola, 4) avoid all health facilities where Ebola patients are being treated if you are not a trained health professional, and 5) wear personal protective equipment if visiting Ebola patients and properly dispose of contaminated items (CDC, 2014).

Control

Proper control measures during an Ebola epidemic also focus on stopping the chain of transmission but they operate after a transmission event resulting in human infection has occurred. For example, control measures involve: 1) active and efficient contact tracing and monitoring, 2) creation of efficient logistical chains to transport samples to laboratories capable of conducting proper analysis techniques on suspected Ebola samples, 3) hiring, training and paying of burial teams to dispose of corpses infected with Ebola, 4) enacting appropriate infection control protocol in all clinics, hospitals and treatment centers, 5) discouraging unnecessary contact and travel during active Ebola epidemics, 6) closing of schools, churches and other large community gathering places where widespread transmission could easily occur, 7) preventing air travel of those who have been exposed to the virus for 21 days, and 8) managing hysteria, fear and violence that can be generated by Ebola epidemics.

Contact tracing is defined as the identification and follow-up of individuals who may have come in contact with an infected person or contaminated body fluids (WHO, 2014). For the purposes of an Ebola epidemic, contact tracing involves the identification of all individuals who may have come in contact with confirmed, probable and suspected Ebola cases. Those conducting contract tracing should avoid shaking hands with potential contacts, maintain a

distance of three feet from potential contacts at all times and use hand-sanitizers frequently. Once contacts are traced, they should be observed for 21 days from the last day of contact with the potential case with their temperatures taken twice a day by staff and transported immediately to available treatment centers when they develop symptoms of disease. Active and efficient contact tracing involves an assessment of the percentage of estimated contacts who are found and put under observation, combined with the speed with which this was done. See Appendix 1 for WHO's technical guidelines on contact tracing during an epidemic of EVD.

The creation of sufficient and efficient logistical supply chains for the movement of samples to laboratory facilities for testing is an essential step in the control of an Ebola epidemic. Prior to the epidemic in West Africa, there were few laboratories capable of conducting the kind of testing needed to determine the presence of infection with Ebola virus in blood samples. The standard laboratory test for Ebola is a reverse-transcriptase polymerase chain reaction, or RT-PCR test and takes 2-6 hours to process at a cost of $100 per sample—covered by WHO (WHO, 2014). As a result, laboratory testing at the outset of the emergency was difficult, expensive and time-consuming since samples had to be transported and the results were often not received for several days. Therefore, mobile laboratories like the one set up by the United States Navy in Monrovia in September 2014, were strategically located throughout Sierra Leone, Liberia and Guinea in order to reduce the time between when a blood sample was taken and results received (*US troops race to stem Ebola outbreak in Africa*, 2014). Faster test results potentially mean better health outcomes as has been indicated by a recent research study conducted on Ebola patients in Liberia (Chertow et al., 2014). In light of this, the WHO launched an initiative to encourage the development of a rapid diagnostic test (RDT) for the Ebola virus that would

reduce the time needed for diagnosis to less than 30 minutes (WHO, 2014). To date, no test meeting these requirements has been developed.

During the ongoing Ebola epidemic in West Africa, understaffed hospitals and clinics could not keep up with the growing number of deaths forcing national Ministries of Health and international agencies to hire and train burial teams to properly dispose of the bodies of Ebola victims. This proved to be especially important in controlling transmission during this epidemic due to local funeral practices that involve the washing and preparing of a body for burial that can lead to mass exposure to the virus within a family or community. However, working on an Ebola burial team is a dangerous position and workers often claimed to be underpaid and underappreciated. In November, burial teams in Sierra Leone went on strike claiming that the government had not paid their $100 per week hazard pay for seven weeks (Fofana and Smith-Spark, 2014). The infectious bodies of Ebola victims were left in the streets and at the entrances of hospitals for several days before burial teams from the Red Cross were called (Fofana and Smith-Spark, 2014).

Since hospitals and clinics have played a major role in the transmission of the virus in previous Ebola epidemics, establishing and implementing appropriate infection control practices in all facilities that could potentially receive Ebola patients is a critical containment measure. In areas experiencing Ebola transmission, all healthcare facilities should build a dedicated triage area at the entrance that is staffed by a nurse or doctor trained in infection control practices. Every patient should be assessed for the presence of Ebola symptoms by a doctor or nurse wearing a suit and gown, gloves and a face shield—further personal protective equipment is required for working with confirmed Ebola cases (WHO, 2014). Suspected and confirmed Ebola cases should be placed in isolation rooms with access to a latrine and running water. If isolation

rooms are unavailable, suspected and confirmed Ebola cases should be placed in separate rooms and staff should be assigned exclusively to this ward. Visitors should be discouraged where possible, screened for symptoms and required to maintain a three foot distance from Ebola patients at all time. Ideally, they should also wear personal protective equipment but this is rarely possible due to insufficient quantities of such gear (WHO, 2014).

A major part of proper infection control in hospitals, treatment centers and public spaces during an active Ebola epidemic involve the disinfection and/or destruction of contaminated articles and surfaces. Methods of disinfection include: heat, bleach and other household disinfectants. In order to disinfect with heat, objects need to be boiled for 5 minutes or heated to 60ºC for 30-60 minutes. The virus is susceptible to the following solutions: 3% acetic acid, 1% glutaraldehyde, and 1:10 dilution of 5.25% liquid bleach or bleaching powder. In areas experiencing Ebola transmission, all healthcare facilities should build a dedicated triage area at the entrance that is staffed by a nurse or doctor trained in infection control practices.

Infection control practices require all healthcare personnel to wear appropriate personal protective equipment (PPE). PPE is defined as specialized clothing and equipment worn to protect against infectious materials (CDC, 2014). PPE for working with a level 4 pathogen like Ebola virus should be put on in a dedicated changing room under the supervision of a trained colleague and should include: double gloves (nitrile preferred), a disposable gown, a disposable waterproof apron, a non-collapsible surgical mask, goggles or face shield, waterproof boots, and a fluid-resistant particulate respirator if procedures that generate aerosols are conducted (WHO, 2014). When exiting the isolation area, workers should: carefully remove and dispose of PPE into waste containers, being careful to prevent soiled items from coming in contact with skin, not recycle single-use PPE, and carefully disinfect reusable equipment. Additionally, it is important

that PPE is removed under the supervision of a trained colleague to ensure that proper protocol is followed and contamination does not occur. When Ebola patients die in a healthcare facility, handling of the remains should be kept to a minimum, as the body fluids can remain infectious for several weeks. Remains should be placed in a double bag; the entire surface should be disinfected, sealed, labeled as infectious material and immediately moved to a mortuary or cemetery for disposal (WHO, 2014).

During the West African Ebola epidemic, several additional control measures had to be implemented to help slow transmission of the virus. Health educators discouraged unnecessary contact and travel, while government officials instituted curfews and closed schools, churches and other large community gathering centers where widespread transmission could easily occur. Schools reopened in January 2015 in Guinea and mid-February 2015 in Liberia after a six-month closure. Schools are scheduled to reopen in Sierra Leone in March 2015 (*Ebola crisis: Sierra Leone to reopen schools in March,* 2015). Another major containment strategy to prevent transmission of the Ebola virus outside of West Africa has been to prohibit travel in people who have been exposed to the virus. Before boarding an international flight, all three West African countries have been requiring citizens to sign a document verifying they have not been exposed to the virus (WHO, 2014).

One of the most difficult aspects of control during Ebola epidemics involves the management of fear, hysteria and violence that can develop as a result of the uncertainty and high mortality associated with the virus. In Guinea, Sierra Leone and Liberia, much of the population knew little about the virus prior to the epidemic that has devastated their countries. This has played a major role in the difficulty of containing the spread of the virus as education teams had to be sent out to sensitize local populations about the existence of the virus and how it

was spread (WHO, 2014). The lack of knowledge regarding the virus, combined with a deep mistrust of the government among citizens in these three countries due to decades of civil war, dictatorship and corruption set the stage for a difficult response effort (Mark, 2014). Fear of quarantine caused some to hide themselves or sick relatives, fear of contracting the virus caused many healthcare workers to flee their posts in countries already suffering from significant shortages of health staff, and fear of starving to death due to border closures and curfews caused citizens to disregard important control measures (Bellone, 2014). Fear of the disease was further incensed by the lack of sensitivity in the approach taken to educate rural communities by foreigners in biosafety suits and national curfews enforced by armed soldiers (Hay, 2014). These combined factors led to a further deterioration of trust and multiple instances of violence against medical and educational teams sent into rural communities (WHO, 2014).

Chapter 7: The Role of the Media in the Current Epidemic

In any emergency situation, risk communication is essential to provide up-to-date information and create trust between the major actors (usually the government, a United Nations agency or some combination thereof) and the general public. What determines good risk communication varies between organizations. According to the World Health Organization, good risk communication in emergencies involves: 1) transparency and early announcement of a real or potential risk, 2) public communication coordination, 3) information dissemination including media relations, and 4) listening through dialogue (WHO, 2014). Or, more simply, the Crisis Emergency Risk Communication (CERC) principles developed by the CDC suggest that you: be first, be right, be credible, express empathy, promote action and show respect (CDC, 2014). As detailed in the previous chapter, the West African epidemic erupted in a region with little to no prior knowledge of Ebola Virus Disease and a deep mistrust of the government. These factors, combined with the slow start of the national and international response effort, allowed rumors and misinformation to spread throughout the affected West African nations. The media, both within West Africa and in Westernized countries, sensationalized the risk and fed the fear and hysteria that developed in areas where Ebola patients were treated. This chapter first details the role of the media in the West African response, followed by the role of the media in Westernized nations with little risk of Ebola transmission.

The best way to gain trust and to communicate effectively in an emergency situation is to have established a certain level of trust with the public and to have a risk communication strategy in place prior to the start of an epidemic. However, that trust and pre-determined strategy had not been developed in Guinea. Three months passed between the first case of Ebola in Guinea and

the notification of the Ministry of Health and ultimately the World Health Organization. This fact alone can explain much of the fear and misinformation that contributed to the extreme difficulty of gaining control of the epidemic. Southeastern Guinea had seen dozens of people die of an unknown disease and it didn't take long for Guineans to observe that the disease often spread after healthcare workers visited their remote villages or local villagers sought care in nearby cities. This combined with the high number of healthcare worker deaths from Ebola, especially early on in the epidemic, led to rumors that healthcare workers were responsible for spreading the illness and violence against medical teams such as attacks, destruction of vehicles and equipment and even murder resulted (WHO, 2014). This fear and misinformation culminated in an attack on a team of health workers, local officials and journalists that resulted in eight deaths (BBC, 2014). Misinformation regarding prevention and treatment methods also spread quickly at the beginning of the epidemic with text messages and twitter posts claiming that products ranging from coffee with milk to onions could prevent infection with the virus (Mark, 2014).

By the time epidemiologists had traced the hotspot for the spread of the Ebola virus within Sierra Leone to the city of Pujeh, they faced significant challenges in slowing its spread. A local doctor explained, "The people living in these areas said there's no such thing as Ebola. They have their traditional beliefs and their traditional cures and they look up to their traditional leaders. Until we can bring the traditional leaders onside, it will be very difficult to convince them that Ebola even exists" (Mark, 2014). This statement proved true to a large extent for the entire region since an effective risk communication was not immediately employed and the response effort had to constantly address misinformation, rumors and a frightened populace. When Ebola struck Kailahun district, neighboring the city of Pujeh, it was initially seen as a

conspiracy by the government of Sierra Leone to depopulate the district and response efforts met with violent opposition (Mark, 2014). As a result, the weekly case counts for the district continued to climb week after week until health teams and local leaders were finally able to convince locals that Ebola was a very real, but preventable disease. After this, weekly case counts dropped significantly as people began to seek care when they developed symptoms and to follow important infection control measures. The MSF project coordinator in the district, David Nash, explained that the "acceptance of the community and the acknowledgement that Ebola is real" made all the difference "in order to come to this point" (WHO, 2014).

Months after the virus first spread to Liberia from Guinea, many Liberians still believed that it was a hoax created by the government to divert attention from several recent political scandals. A Liberian student named Alfred Randall went so far as to say, "the government of Liberia has come up with a new strategy to divert the Liberian people's mind. We understand the issue of Ebola, Ebola is real, we agree the virus is a very terrible virus, but Ebola is not in Liberia" (Mark, 2014). The MOH for Liberia finally began publishing graphic and disturbing images of Ebola victims in newspapers and on television in order to demonstrate to citizens that it was a real disease with devastating health consequences that cannot be cured through prayer or traditional healing (Mark, 2014).

Although the Ebola response faced many challenges to risk communication at the outset of the epidemic, eventually accurate information was spread rapidly and lines of communication were opened between citizens with questions regarding the virus and its spread and scientists and researchers who could best answer those questions. The most effective methods to communicate information regarding the Ebola virus during the epidemic in West Africa were: mass text messages, social media (e.g Twitter and Facebook) and posters. The use of mass text messages,

also known as short message service (SMS), has become a popular tool around the world for communicating information rapidly since many countries have more cell lines than there are people and even the most rural people in developing countries often have cell phones (Ogunlesi, 2012). The use of SMS messages allowed the national and international response to send short, but accurate information regarding the epidemic to people around the country. Cell phones have also greatly increased access to the Internet due to many phones now having the capability of connecting to the web. Therefore, the governments of the countries experiencing cases or who were at risk of imported cases were able to spread accurate information and longer messages this way that were seen by large numbers of people. Twitter and Facebook are both platforms that also allowed for officials and communication teams to respond to inaccurate information that was circulating in a quick and effective manner. Finally, the development of posters and written materials that rely mainly on pictures so that literacy is not required for comprehension have long been an effective strategy in communities with low literacy rates and/or high numbers of people with no knowledge/denial of a current situation. Community health education teams were another strategy employed during the epidemic to combat misinformation and limited awareness of Ebola Virus Disease. These teams were effective, especially in rural communities cut off from other forms of communication, but they faced often violent and angry communities (WHO, 2014). Another effective method was the creation of songs by West African musicians that passed information regarding how Ebola was transmitted and when/where people should go to seek care (*West African musicians produce their own Ebola appeal song*, 2014). These were the primary tools that were in used in combination with the traditional delivery of press conference and television appearances by government officials aired on the radio and on television but such messages often suffered from a lack of trust in the officials who gave such statements.

In the United States, the situation seemed to develop almost entirely in the opposite way. Instead of spending resources to convince the people at risk that there was a real threat to their health and precautions should be taken, the CDC had to spend an inordinate amount of time and resources trying to convince people that their risk of exposure to the virus—even if cases were being treated in medical facilities within their community—was exceptionally low. Once Thomas Duncan tested positive for the Ebola virus in Dallas, irrational fear erupted in nearby communities demonstrated by: closure of schools to prevent transmission among children, refusal of businesses and schools to allow people who had recently traveled to African countries unaffected by the Ebola epidemic to return to work for several weeks, visa refusal for all West Africans until the epidemic ended, and demands for mandatory isolation of healthcare workers returning from working on the epidemic in West Africa.

Some, like Donald Trump, even went as far as to say that any American healthcare workers who develop Ebola should be treated in West Africa with the best available care rather than airlifted back to the United States for treatment (Connor, 2014). And yet, the CDC and every other health organization repeatedly stated that the risk of Ebola transmission was very low but that even if a case did occur, the US had the resources and knowledge to implement proper infection control practices to prevent secondary cases. A survey conducted by the Harvard School of Public Health found that nearly 40% of Americans believe that there will be a "large outbreak" of Ebola in the US and that they are concerned that an immediate family member will become infected in the next year (Fox, 2014). To date, there have been 10 cases of Ebola treated or acquired in the United States, 8 of whom recovered from the virus. Two of the ten cases were contracted on US soil in nurses who treated Thomas Duncan in Dallas without proper infection control practices in place. So why is there such a disconnect between perceived risk and actual

risk in the case of Ebola in the United States? Maggie Fox, working for NBC News, writes that it might be the media's fault (Fox, 2014). The constant media coverage of the Ebola epidemic and inflated articles about what it would mean for Ebola to come to the US led many Americans to believe that the level of risk was much higher than it was. Article titles like Newsweek's "Smuggled Bushmeat is Ebola's Back Door to America" continued to feed an already overinflated level of risk (Flynn and Scutti, 2014).

The problem with fear, however, is that regardless of its rationality it must be addressed. When the CDC followed the best risk communication strategy of stating what is known, stating what is not known and stating what is being done to fill in the knowledge gaps when Thomas Duncan tested positive for Ebola, the public already had an escalated perception and fear of the risk this posed to American communities. Further, the CDC confidently stated that American hospitals were completely capable of safely treating Ebola patients. When two nurses treating an Ebola patient in Dallas became infected, this seriously damaged their credibility (Rosenbaum, 2015). However, the CDC was not incorrect. American hospitals with proper infection control protocols in place are capable of managing Ebola cases—Texas Health Presbyterian Hospital where these two nurses were infected proved to have insufficient and ambiguous protocols in place during the treatment of Thomas Duncan.

Further, everyone looked to the CDC to handle the Ebola situation in the US when they were already overtaxed in efforts to respond to the real Ebola crisis in West Africa. A recent report released by the Presidential Commission for the Study of Bioethical Issues extensively criticized the financial and personnel resources that were necessary to respond to Ebola in the United States consequently diverting those resources from where they were most needed in West Africa (*Ethics and Ebola: Public Health Planning and Response*, 2015). In other words,

mandatory quarantine for Ebola workers in order to make American's feel safer can actually pose a greater threat if they inhibit the ability of American healthcare workers to assist in the response in West Africa, thereby lengthening the amount of time and financial resources necessary to bring the epidemic under control there (Rosenbaum, 2015). The excessive coverage, selfish slanting of Ebola news as to how it affected Americans and the sensationalizing of the Ebola epidemic in the American media had detrimental consequences both for West Africans and American citizens.

Chapter 8: Vaccine & Treatment Possibilities

Vaccines

Chimpanzee adenovirus serotype 3 vaccine (CAd3)

CAd3 is a recombinant vaccine that uses chimpanzee adenovirus 3 with the surface proteins for both the Sudan and Zaire strains of the Ebola virus inserted into it. The vaccine, developed by the British pharmaceutical company GlaxoSmithKline, entered Phase I clinical trials in September 2014 in Oxford and Bethesda. Additional trials are being conducted in Switzerland and Mali. In a study conducted on monkeys, all 16 were protected by a single dose of the vaccine after being administered a lethal dose of Ebola (WHO, 2014). This vaccine type has been successfully and safely used in humans for other diseases and preliminary results from the US trial show that it was well tolerated and produced both an antibody and a cell-mediated immune response in all 20 volunteers (ECDC, 2015). Phase II and Phase III trials of CAd3 vaccine began in several African countries in early 2015.

Recombinant Vesicular Stomatitis Virus vaccine (rVSV)

rVSV is also a recombinant vaccine that uses a vesicular stomatitis virus with a glycoprotein of the Ebola virus inserted into it. rVSV vaccines have shown 100% efficacy in non-human primates when administered a lethal dose of several different filoviruses 28-35 days after a single dose of the vaccine (Mire et al, 2014). A more recent study demonstrated that the protection period may be much longer, as an rVSV vaccine against Marburg showed 100% efficacy in non-human primates when administered a lethal dose of Marburg virus fourteen months after a single dose of the vaccine (Mire et al, 2014). This vaccine could potentially play

an important role in providing a vaccine for people who live in high-risk rural areas as well as helping to shorten filovirus epidemics. Unfortunately, rVSV vaccines have not been used in humans and the WHO expressed many concerns with using this vaccine type against Ebola including: it is unknown whether rVSV-EVD will grow in humans (especially those with weak immune systems), the efficacious amount is unknown (too weak of a vaccine could produce an insufficient response while too strong of a vaccine could cause illness), and the side effects of the vaccine in humans are unknown (WHO, 2014). The vaccine, developed by NewLink Genetics and now produced by Merck, entered Phase I clinical trials in late 2014 in Germany, Switzerland, UK, US, and Kenya (ECDC, 2015). The trials were put on hold in December 2014 after several volunteers developed minor joint pain; however, they were resumed in early January with a lower dose of the vaccine (ECDC, 2015). Phase II and Phase III trials of rVSV vaccine began in several African countries in early 2015.

Three different Phase III trial strategies are being implemented in Guinea, Sierra Leone and Liberia. The first is a ring vaccination trial in Guinea, conducted by the WHO and MSF. This is an older vaccination strategy that was used in the eradication of smallpox by finding the newest cases and vaccinating contacts in a ring around those cases (like a village or neighborhood) in an attempt to stop the chain of transmission. The Liberian government, NIH and the US are collaborating on a randomized controlled trial in Liberia with three arms—one arm for each of the two best vaccine candidates (rVSV and Cad3) and a comparison arm that will receive neither vaccine. Participants are recruited from the general population in Monrovia and NIH hopes to recruit 10,000 participants in each arm of the study (Enserink, 2015). Meanwhile, in Sierra Leone, the government—in collaboration with the US and the CDC—is conducting a stepped-wedge trial of healthcare workers at Ebola treatment units where everyone receives the

vaccine but at different time intervals so that time to infection can be assessed (WHO, 2015). Each trial is assessing the efficacy of a single dose of one or both of these vaccine candidates. However, the significant decline in the number of new cases of Ebola (while great news for West Africa and the response effort) is making it difficult for the vaccine trials to enroll enough participants to show any significant protection factor from the vaccines (WHO, 2015).

Ad26-ZEBOV + multivalent MVA-ebola virus

Johnson & Johnson developed this vaccine, a later player on the Ebola vaccine stage, with AdVac technology from Crucell Holland and MVA-BN technology from Bavarian Nordic (ECDC, 2015). Unlike the other two vaccine candidates, this one will require a two-dose series—the first of which primes the immune system and the second provides a booster dose. This vaccine entered Phase I clinical trials in the UK in early January 2015. It is unlikely, however, that efficacy data will be available in time for this vaccine to be fast-tracked for the Ebola epidemic (WHO, 2015).

Treatments

No proven treatment courses for Ebola existed prior to the West African epidemic and no new treatment methods have been shown to be significantly effective in reducing mortality from the virus. However, several drugs show promise and a few have been administered to Ebola patients under emergency authorization of the Food and Drug Administration (FDA) in the US. All patients who receive experimental drugs sign waivers acknowledging the danger of receiving treatments that have not gone through the entire safety and efficacy testing normally required.

TKM-Ebola

TKM-Ebola is an experimental RNAi therapeutic drug developed by Tekmira Pharmaceuticals Corporation that acts by targeting three of seven proteins in an Ebola virus. After demonstrating promise in limiting infection in non-human primates, TKM-Ebola entered Phase I clinical trials in the United States. It was placed on a partial hold after several volunteers developed gastrointestinal illness after receiving the drug. However, that still allows it to be used in the treatment of human patients with suspected or confirmed infection with Ebola (Tekmira, 2014). TKM-Ebola has developed a new variation of the drug thought to be more effective against the Ebola strain circulating in West Africa and clinical trials are expected to begin in early 2015 (Tekmira, 2014). TKM-Ebola was used in the treatment of American doctor Richard Sacra who recovered from the virus. American nurse, Nina Pham, also received TKM-Ebola and recovered from the virus.

AVI 7537

AVI 7537 attacks one of the three genes that TKM-Ebola also targets, but in a very different chemical way and works to prevent viral protein from being produced. The drug has shown promise in treatment of both guinea pigs and monkeys with 83% survival if administered within 48 hours of exposure and 67% survival if administered within 72 hours of exposure to the Ebola virus (WHO, 2014). The drug is available in small amounts but has not been used in the treatment of any human Ebola patients to date.

BCX4430

BCX4430 is a viral RNA-dependent RNA polymerase inhibitor discovered by BioCryst Pharmaceuticals developed for use as a broad-spectrum antiviral treatment. After showing promise in preventing infection with Ebola and Marburg viruses in non-human primates up to 48

hours after exposure, BCX4430 entered a dose ranging efficacy study in late 2014. If successful, the drug would meet the FDA's Animal Rule—allowing it to be used for emergency treatment in humans while parallel human safety trials are also being conducted (Kroll, 2014). To date, BCX4430 has not been used in the treatment of human Ebola patients.

Brincidofovir

Brincidofovir, an antiviral oral drug developed to treat viruses such as Cytomegalovirus and Small Pox by Chimerix Inc., has shown some promise in the treatment of Ebola Virus Disease (even though Ebola is not a DNA virus, which the drug has been developed to work against). Since it was already in Phase III clinical trials for treatment of Cytomegalovirus and adenovirus, the FDA granted it emergency authorization for use in the treatment of Ebola cases Loftus, 2015). It was administered to Thomas Eric Duncan, a Liberian national who became the first person to be diagnosed with Ebola in the US after exposure in Liberia. He did not recover from the virus. American journalist, Ashoka Mukpo, also received Brincidofovir and did recover from the virus (CFR 50%). A Phase II clinical trial started in January 2015 in Liberia but was soon discontinued due to an inability to enroll enough subjects (Loftus, 2015).

Favipivavir

Favipivavir is an approved Influenza treatment course in Japan. It demonstrated protection against Ebola in mice; however, protection was much lower in monkeys. Additionally, although the drug is safe and highly available for use, the dosage that would be required for treatment of Ebola is much higher than previously tested efficacious amounts and so is still considered an experimental treatment course for Ebola patients. Favipivavir was given to Spanish nurse Maria Teresa Romero Ramos and she recovered from the virus.

Interferons

Interferons are the first immune response of the cell. They stimulate the immune system to amplify the response to pathogens. Treatment with interferons has been used effectively to amplify the body's response to diseases like hepatitis and multiple sclerosis. Studies conducted on monkeys have shown a delayed time till death from Ebola, but no effect on survival rates (WHO, 2014). Additionally, there are several different types of interferons and further research would need to be conducted on which to use, when to administer them and efficacious dosage amounts for this to be considered a potential Ebola treatment.

ZMapp

ZMapp is a drug cocktail containing three different monoclonal antibodies that have shown 100% efficacy in fighting Ebola infection in rhesus macaques with both minor infection and signs of advanced disease (Qiu et al, 2014). The antibodies in the cocktail seek out Ebola viruses in the body and neutralize them, potentially limiting infection severity and length. In order to produce the three antibodies in the ZMapp cocktail, tobacco plants are infected with a genetically engineered virus and the antibodies produced by the immune response are harvested from the leaves (Qiu et al, 2014). Unfortunately, it takes several months to grow, infect and produce the drug cocktail and only a few doses were available at the time of the West African epidemic. The first two Americans to be treated for Ebola in the US, Nancy Writebol and Dr. Kent Brantly, both received ZMapp and recovered from the virus. Three healthcare workers in Liberia received ZMapp and two of the three recovered from the virus. A British nurse received the drug and recovered from the virus. A Spanish priest received the drug and did not recover from the virus. To date, of the seven people who received ZMapp, 2 have died of Ebola infection (CFR 29%). Researchers working on the drug believe that this is due to either genetic variation

that result in increased susceptibility to the virus and/or delays in receiving the treatment. Since the treatment is a three dose series administered over a nine day period, researchers believe that delays in receiving ZMapp treatment for the two cases who died resulted in a too advanced stage of the disease to be reversed (Qiu et al, 2014).

ZMab is a precursor to the drug ZMapp and although it showed efficacy in treating infection in non-human primates with Ebola, ZMapp was created as a better and more effective combination of six possible antibodies. A Norwegian doctor working for MSF in Sierra Leone was given the drug and recovered from the virus. An elderly patient was given the drug in Sierra Leone and also recovered from the virus. A Cuban doctor received the treatment in Switzerland after developing infection in Sierra Leone and recovered from the virus. An Italian nursing assistant who developed Ebola in Italy while assisting in the treatment of two infection Spanish missionaries received either ZMapp or ZMab (reports are inconsistent) and recovered from the virus (Sheets, 2014; Branswell, 2014).

Plasma Transfusions from Ebola Survivors

Plasma is the yellow serum that is left after filtering red blood cells from donated blood. It contains the immune response to viruses such as antibodies and has been used successfully for decades to help kick start a person's immune response certain infections such as Influenza. In the case of Ebola, it is not known whether transfusion with the plasma of a survivor has a significant effect on a patient's ability to fight infection. However, it is considered to be a promising treatment option and has been used both within West Africa and the United States but with unknown success because no clinical trials have been conducted.

In order for someone to be considered a potential donor of plasma for Ebola treatment purposes, the WHO has created a list of requirements that must be met, including: patient must

have recovered from EVD and been released from a treatment center at least 28 days ago, patient must have been released with no clinical symptoms of infection, patient must have tested negative for Ebola virus RNA using molecular techniques at least 24 hours apart to ensure he or she is free of infection, and patient must meet health and age requirements for blood donation within the country (WHO, 2014). Donated blood must then been filtered, cleaned and checked for any other potential pathogens. In February of 2015, Emory University began collecting blood donations from Ebola survivors, especially those who were treated in the US. To date, 18 units of plasma have been collected in Atlanta for research purposes and in the event that further aid workers are infected with the virus in West Africa and flown to the US for treatment. The program hopes to answer many different research questions regarding plasma transfusion for Ebola including: 1) do some patients produce more antibodies, making them better donors? 2) Can the antibodies and other important cells of the immune response be filtered out and used to create experimental drugs? 3) Can plasma be freeze-dried and reconstituted, making it easier to distribute it where it is needed (Fox, 2015)? A parallel program collecting plasma at the ELWA2 hospital in Monrovia, Liberia is also running a clinical trial enrolling up to 70 Ebola patients—some of whom will receive plasma transfusions, while the control group (comprised of patients who have blood types incompatible with any of the available plasma) will receive the same level of care but no plasma transfusions (Butler, 2014). The first patient was enrolled in this trial in late December and results are expected within a few months. A similar trial started in Guinea in early January and hopes to enroll between 200 and 300 patients assessing survival rates after 2 weeks for treatment versus non-treatment groups. Sierra Leone hopes to conduct a similar trial soon. These clinical trials are important in determining whether transfusion with the plasma of an

Ebola survivor has a significant effect on the survival rate and also what the optimal dose is and how frequently plasma should be administered (Butler, 2014).

Hyperimmune globulin, prepared from the plasma of donors with high levels of antibody response to a pathogen, is also considered a possible pre and post-exposure treatment for Ebola as it has been successfully used against organisms such as rabies. It works by providing instantaneous short-term immunity to a pathogen and has been demonstrated to be effective in monkeys if received within 48 hours after exposure. However, hyperimmune globulin is not currently available and although studies are being conducted in both horses and cattle, the product is not expected until mid 2015 (WHO, 2014).

Tetrandrine

Tetrandrine, a compound derived from the root of the Chinese medicinal herb Stephania tetrandra, has undergone laboratory testing and is being considered as a potential prophylactic and/or treatment for Ebola virus infection. The compound works by inhibiting a virus's ability to infect a cell. Viruses must move deep into a cell in order to break out of the endomsomes that transport the virus into a cell and they do this through two-pore channels. Studies conducted on human white blood cells in a laboratory suggest that tetrandrine is capable of blocking two-pore channels so that the virus never passes deep enough within the cell to infect it and is instead destroyed by the cell's immune response (Sakurai et al, 2015). The compound also prevented Ebola virus disease in mice. Further research is being conducted to determine whether the dose required to prevent infection with the virus in the human body would be safe (Dunham, 2015). To date, this compound has not been used in the treatment of human Ebola patients.

Ethical Considerations in Vaccine and Treatment Options

Ethical concerns have been a complicated issue during the entire Ebola response in West Africa. The WHO met on August 11th, 2014 to discuss the ethics involved in the use of unproven treatments and vaccines to combat the Ebola epidemic. They concluded, "In the particular context of the current Ebola epidemic in West Africa, it is ethically acceptable to offer unproven interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans as potential treatment or prevention" (WHO, 2014). They stressed, however, that ethical guidelines should be used to determine the use of all treatment methods including complete transparency regarding the risks involved in unproven treatments, informed consent, freedom of choice and the preservation of dignity and privacy of all patients. In the end, the WHO recommended that plasma from Ebola survivors should be prioritized as the best treatment method for the West African response since it could provide the most readily available treatment in terms of time and quantity. The remaining experimental drugs were sidelined until they could show some efficacy and safety and were available in larger amounts.

However, ethics become complicated when there is an insufficient amount of experimental drugs to treat all of the people who want them. How then do we ethically decide how they are distributed? This issue came to a head when Dr. Kent Brantly and missionary Nancy Writebol became the first Americans transported back to the US for treatment after becoming infected with Ebola while working in West Africa and it was announced that they would be treated with the experimental drug, ZMapp. Many West Africans, and surely many Ebola responders, were left asking, 'what experimental drugs?' and rightfully so. The problem,

however, is much more complicated. Years of federal budget cuts for global and public health spending have decreased available funds to support the production and testing of treatments and vaccines for rare viruses such as Ebola that do not threaten the US directly. Since pharmaceutical companies are generally unwilling to spend the millions of dollars necessary to carry out randomized controlled trials for drugs and vaccines that are rare and therefore do not have the ability to bring in large profits, research on prevention and treatment for Ebola came to a halt. As the Ebola epidemic in West Africa grew further out of control, there were a number of potential treatments that had a few treatment courses available. But what do you do with seven courses of ZMapp against thousands of Ebola cases in West Africa? That being said, I'm not convinced this makes it acceptable for Americans and other Westerners responding to the epidemic to receive experimental drugs that West Africans were never considered for. In fact, many of those who received such drugs would agree. Dr. Ian Crozier, an American doctor who contracted Ebola while working in Sierra Leone, was the sickest patient treated at the Emory University isolation unit. And yet, he did not receive any experimental treatments other than plasma transfusions because they were unavailable at the time. That being said, he received the best medical care that an American hospital can offer and acknowledged his unease with the inequality when he said, "Do I wish my patients that I'd been with just a few days before had access to that type of critical care? Absolutely. Absolutely. That's obviously a difficult thing for me to think and talk about" (Beaubien, 2014).

Perhaps an even greater ethical debate that emerged from the Ebola epidemic is how to carry out randomized controlled trials for potential vaccines and treatments. With scientific proof of efficacy reliant on randomized controlled trials, scientists and public health officials argued over the ethicality of denying potentially life-saving vaccines and treatments from patients who

wind up in the control groups in the case of a disease with such a high case fatality rate just to provide scientific evidence (Presidential Commission for the Study of Bioethical Issues, 2015). At the core, opponents on this issue are in disagreement as to the primary goal of clinical research during a public health emergency. Those who uphold the use of randomized controlled trials in emergency settings believe that the primary goal of clinical research in this setting is to determine safe and efficacious interventions as quickly as possible. For those who believe that randomized controlled trials are unethical and unrealistic in emergency settings, they argue that the main goal of clinical research should be to provide potentially life-saving measures to as many people as possible using scientifically valid research designs (Presidential Commission for the Study of Bioethical Issues, 2015). The debate did not reach a consensus, however, and all of the Phase III trials being conducted in West Africa rely on different research designs.

Chapter 9: Conclusion

By far the largest ever epidemic of Ebola Virus Disease appears to be drawing to a close in West Africa. However, it has entered the most difficult stage—that of total elimination of all Ebola cases in the human population (WHO, 2014). This is difficult given the remoteness of many communities, their poor access to health services and transportation concerns. However, the region contains more hospital beds, laboratories and health staff than it ever did prior to the Ebola epidemic—this fact, combined with the treatment and vaccine trials currently underway in areas where weekly case numbers are still high, finally hints at an end to an Ebola epidemic that infected more than twenty times the number of people of all previous Ebola epidemics combined.

The West African Ebola epidemic had devastating consequences on the region both in terms of lives lost and economic impacts. Therefore, it is even more imperative that the lessons learned should serve to reduce the magnitude and scope of future Ebola and other major infectious disease epidemics. For instance, as a direct result of the West African epidemic, clinical knowledge of Ebola disease has vastly improved—leading to a better understanding of appropriate treatment protocols for future Ebola cases. More specifically, the survival of American doctor Ian Crozier, who had an extremely high viral load and went into organ failure, taught his doctors that aggressive treatment including life-support measures could improve survival in some Ebola patients (Beaubien, 2014). Importantly, this epidemic also highlighted the need for an immediate and efficient response by UN agencies like the WHO to epidemics in other countries, lest they spiral out of control before the international community has even acknowledged the issue. Additionally, this epidemic has significantly increased global awareness

of the Ebola virus and brought it close enough to home to convince many citizens of Westernized nations to financially support efforts to prevent and control future Ebola and other emerging infectious disease epidemics. Researchers who worked on an epidemic of *ebolavirus Bundibugyo* in Uganda several years prior to the West African epidemic concluded that there was a major need for improved surveillance, reporting and diagnostics to prevent further epidemics of this deadly virus (MacNeill et al, 2011). Their advice went unheeded, but perhaps the devastation of many West African communities will at the very least allow appropriate distribution of financial and personnel resources to prevent such an epidemic in the future. Related to this, the Ebola epidemic in West Africa has fostered new partnerships between pharmaceutical companies, researchers and governmental organizations to develop and push through promising treatment and vaccine candidates for Ebola. Although many of these will come too late to be of much use in the current epidemic, they have the potential to protect high-risk communities in Central and West Africa from future Ebola epidemics.

The Ebola epidemic has killed almost 10,000 people. It has had major economic impacts on Guinea, Sierra Leone and Liberia in particular, and the entire region in general. However, it has also been a major lesson to public health officials regarding the importance of global health systems strengthening and what it takes to make many citizens of Western nations care about the dysfunctional state of many African health systems. It should not have taken an imported case in a Dallas hospital and two locally acquired infections in American healthcare workers directly involved in the treatment of the imported case to bring the gravity of this epidemic to the forefront of American politics.

Investments in Guinea's healthcare system would have had several opportunities to change the tide in this epidemic. An increased number of clinics and hospitals would have

expanded access to care and increased the likelihood that the disease would be reported to the ministry of health. An investment in the laboratory capacity of Guinea's health system would have decreased the time needed to isolate and identify the pathogen causing the epidemic as Ebola Virus. It also would have decreased the costs and time involved in having to send further samples from potential Ebola cases to international laboratories. An investment in the communicable disease surveillance system in Guinea would have greatly increased the likelihood of the cases of unknown hemorrhagic fever being reported to the system and investigated by the Ministry of Health months earlier. An investment in the training of healthcare workers in Guinea would have prepared them to respond appropriately by following standard operating procedures for a nationally notifiable disease, significantly decreasing the time between the first few cases and the notification of Guinea's Ministry of Health. Imagine how far the billions of dollars spent on the Ebola response could have gone towards permanent investments in West African healthcare systems.

It shouldn't take a case of Ebola in Dallas for Americans to care about an epidemic that has killed thousands of West Africans. It shouldn't take fear of a pandemic to convince high resource nations to invest in the health infrastructure of low resource nations. If that is what it takes, however, then let us learn the multi-billion dollar lesson well. Let us use the current upsurge of support and funding for global health programs to increase the healthcare and laboratory capacity of low resource nations—leading to improvements in the overall health of those nations and simultaneously increasing their ability to respond to future public health threats. Let us not forget that Ebola "is a disease of poverty, of dysfunctional health systems – and of distrust"—all of which are preventable and reversible states (Brown, 2014).

Chapter 10: Epilogue

In the week leading up to 12 April 2015, the Ebola case count in West Africa increased slightly from the previous week's low of 30 with 37 new cases (28 in Guinea, 9 in Sierra Leone, 0 in Liberia) (WHO, 2015). This brings the total Ebola case count from the West African epidemic to 25,791 as of 12 April with 10,704 deaths (CFR 41.5%). The last case of Ebola in Liberia died on 27 March and no new infections have been reported. If no new cases develop, Liberia will be the first of the three West African countries at the heart of the epidemic to be declared Ebola-free on 8 May, 2015 after 42 days with no new cases of the disease. The World Health Organization estimates that Sierra Leone will not be far behind and that Guinea will be the last country to be declared free of the virus but that it could be as early as mid-summer 2015 (WHO, 2015).

On 13 March 2015, an American doctor working for Partners in Health in Sierra Leone tested positive for Ebola and was flown to Maryland's NIH facility for treatment. Sixteen of his colleagues were also flown home and monitored for symptoms of the virus due to exposure while attempting to help their ill colleague (Fox, 2015). The male patient's identity has not been released, but he recovered from the virus and was discharged from the hospital on 9 April 2015. None of his colleagues developed symptoms of the virus (Fox, 2015).

As weekly Ebola case counts continue to decline rapidly in West Africa, the WHO acknowledges that little information may come from the three vaccine trials currently underway in Liberia, Guinea and Sierra Leone. Perhaps the greatest hope for the vaccine trials is the ring vaccination trial being conducted in Guinea with the rVSV vaccine produced by NewLink Genetics and Merck Pharmaceuticals. The WHO hopes that this Phase III trial will be able to

deliver some results before the end of the epidemic as compared to the other two vaccine trials as a result of: 1) the location of the trial in Guinea—since Guinea's case count has gone done more slowly and the virus us still spreading in the capital, this trial is at an advantage over those being conducted in Sierra Leone and Liberia, and 2) the ring vaccination strategy being used has the ability a great ability to determine effectiveness as high risk contacts of confirmed cases are vaccinated in an attempt to produce a circle of immunity around that case (WHO, 2015).

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