EBOLA VIRUS DISEASE AND THE 2014 OUTBREAK: A LITERATURE REVIEW

by

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Abstract

The Ebola outbreak in West Africa that started in December 2013 has sickened more than 25,000 people and taken more than 10,000 lives, making it the largest Ebola outbreak ever recorded. A review of the chronology of transmission of disease in Guinea, Liberia, and Sierra Leone juxtaposed with the containment efforts of the Ministers of Health, The World Health Organization and Médecins Sans Frontières (MSF) reveal fissures in the response of the global community contributed to the spread of the disease. Ebola failed to be contained quickly because there was: a lack of an coordinated and robust containment program, an inherent distrust in the government and their ancillary Ebola warnings, widespread fear of Ebola Treatment Centers and subsequent hiding of patients, a highly mobile population, the appearance of the disease in urban centers. While the disease has caused widespread morbidity and mortality and destroyed communities and the health care infrastructure, Ebola has given the global health community the opportunity to rebuild health systems and test experimental therapies that can prevent future epidemics from causing widespread devastation and loss of life.

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Background (1)

On December 2, 2013, in Gueckedou, a city of approximately 250,000 people in southern Guinea, a two-year old boy from the Meliandou Village came down with what was probably assumed to be cholera or Lassa fever (4). He exhibited classic symptoms of both diseases: he had a fever, he was vomiting and he had diarrhea. To the best of anyone's knowledge, no outside care was sought on his behalf and he was most likely cared for by his mother at home. On December 6, 2013, a mere four days after he first showed symptoms, the boy died.

Ten days later, the little boy's mother was dead; two weeks after that his sister and his grandmother had both died. All three exhibited the same symptoms as the two-year old boy: vomiting, black diarrhea and fever, all of which came on only a few days prior to their deaths. By the end of December, the entire family, save the father, was gone. The cause of death was never definitively ascertained, but whatever it was, it was killing its victims rapidly.

One month after the two-year old's family was wiped out, a nurse and midwife from Meliandou also developed the exact same symptoms and both died. It is unknown how they contracted the disease, although they have been linked to both the boy's sister and grandmother: it is assumed that they were the caregivers to both. This is a plausible explanation considering that after the mother of the boy died, there was no one else to look after them as they lay dying, so the village caregivers stepped in.

The disease did not stay confined to this one village for long. In Dawa Village, also in the city Gueckedou, the grandmother's sister and at least two other women became ill a few weeks after they attended the grandmother's funeral. All three of these

new cases had symptoms consistent with Ebola and they died five to six days after they fell ill. It is hypothesized that they became infected at the grandmother's funeral, where ritual washing, touching and kissing of the corpse are common traditional burial practices (2). In addition to these three cases, it is thought that up to eight people in Dawa died through exposure at the grandmother's funeral. There were also 14 more deaths in the Baladou District of Gueckedou, all of which were possibly linked to contact with the women who attended the funeral.

The disease left Meliandou village through another route as well. The midwife, who is thought to have cared for the family of the index case back in December, was herself cared for by a member of her own family, who lived in nearby Dandou Pombo Village, also in the city of Gueckedou. One of the midwife's family members became infected while caring for her and took the disease back home to Dandou where it spread to six other people, all of whom later died. The midwife is also suspected of transmitting disease to acquaintances who lived in the Ghandou Village of Gueckedou where three deaths occurred.

Although the midwife was initially cared for by family members at home, she did seek professional medical care. She was admitted into Gueckedou Hospital, a government-run facility in the heart of the city. She was initially diagnosed with cholera (3); as a result unsuspecting staff had unprotected contact with her bodily fluids through the course of treatment. The midwife died in the hospital on February 10, 2014, but not before she infected at least one health care worker who was employed there.

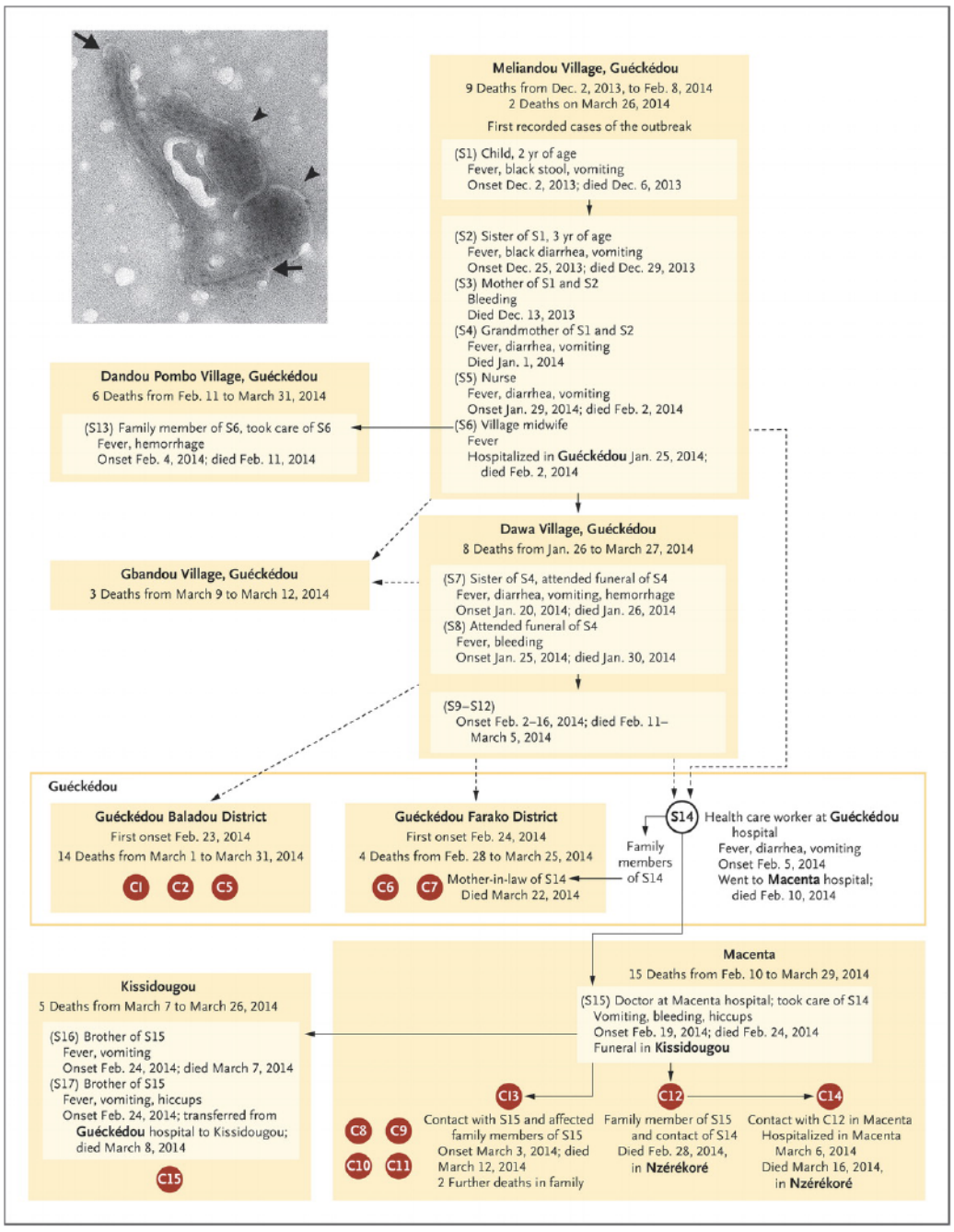
When this heath care worker became ill, she was treated at Macenta Hospital, in Macenta, Guinea, a city 89.5 km (55 miles) to the east of Gueckedou, where she died on

February 19, 2014. During her course of treatment at the hospital, she infected her mother in law who lived in the Farako District of Gueckendou, as well as the doctor who was caring for her in the hospital. It is unknown how many other nosocomial transmissions occurred at Macenta Hospital from this one infected health care worker from Gueckedou Hospital, but at least 15 people, from the middle of February to the end of March, are thought to have been infected by her and died.

The doctor who treated the health care worker in Macenta Hospital transmitted the disease to a person who had contact with him at some point while he was infectious. It is unclear if this was a hospital worker, family member or friend. Nonetheless, this infected person transmitted the disease to two people in his own family (both of whom died by the middle of March) as well as another one of his family members who lived in Nzerekore, a city 84 miles south of Macenta. This family member died in Nzerekore on February 28, 2014. The deceased family member transmitted the virus to a friend, who was hospitalized in Macenta, but died in Nzerekore on March 16, 2014. Finally, the Doctor also transmitted the disease to two of his brothers, both of whom died in the first week of March, in the city of Kissidougou, a city 134 km North of Macenta. See Figures One and Two for a map of the region and a flow chart of transmission patterns.

Source: http://www.nejm.org/doi/full/10.1056/NEJMoa1404505

Figure One: (1) Map of Guinea that highlights the main cites involved at the beginning of the West African Ebola Outbreak of 2014. The outbreak began in a village located within the city of Gueckedou, located where the borders of Guinea, Liberia and Sierra Leone converge. This area is highly trafficked by foot and by car, and the borders are relatively porous, allowing for unfettered movement amongst the three countries (4). Families travel back and forth for commercial purposes and to shop at markets (5). Gueckedou in particular is known for its weekly market that attracts traders from neighboring countries (107). People also cross borders for personal reasons, to attend funerals and family gatherings (218).



Source: http://www.nejm.org/doi/full/10.1056/NEJMoa1404505

Figure Two (1) Transmission Chains of laboratory confirmed cases in Guinea. Dashed arrows indicate presumed links. Laboratory-confirmed cases Aare shown in red circles; suspected cases (S) are identified by case number.

And so the West Africa Ebola Epidemic of 2014 began. On March 10 2014, three months after the index case died, local public health officials in Gueckedou and Macenta alerted the Ministry of Health in Guinea and Medicins sans Frontieres (Doctors Without Borders) who already had a team on the ground that was working in Gueckedou on a malaria project (3; 208) about this mysterious disease characterized by fever, vomiting and diarrhea (1; 2; 3). On March 14 a health ministry team was sent to Gueckendou to investigate. Medicins sans Frontieres (MSF) also sent a team that arrived on March 18. Within a fortnight, BSL4 laboratories in Lyon, France and Hamburg, Germany identified the causative agent as Zaire Ebolavirus. On March 23, 2014, the World Health Organization in Geneva was officially notified of the outbreak (1).

Although the disease percolated in the remote forested regions of Guinea for the first few months of 2014, it did not take long for the virus to find its way into urban areas. On approximately March 31, 2014 the first Ebola cases were recorded in Conkary, the capital of Guinea, home to approximately two million people (210; 211). By this time there were also 80 suspected cases and 59 deaths in Gueckedou; 23 suspected cases and 15 deaths in Macenta; and eight suspected cases and five deaths in Kissidougou (7).

Despite MSF warnings during the late winter and and early spring of 2014 that the epidemic was "of a magnitude never before seen in terms of the distribution of cases in the country," (7) it wasn't until July 22, 2014 that Dr. Louis Sambo, the Regional Director of the WHO West African Office visited the affected regions (8; 152). By this time, there were 415 cases and 314 deaths in Guinea; 224 cases and 127 deaths in Liberia; 454 cases and 219 deaths in Sierra Leone; for a total of 1093 cases and 660 deaths across the region (8).

On August 8, 2014, eight months after the epidemic began, after 961 people had died and 1779 cases were recorded (160), the WHO finally declared the epidemic to be a "public health emergency of international concern" (9).

The 2014 Ebola outbreak is unprecedented in terms of its scope and size. It has lasted longer than all other previous outbreaks, and is the largest Ebola outbreak ever recorded. What started as a handful of cases in rural southeastern Guinea eventually spread to urban centers and capital cities in Sierra Leone, Liberia, Senegal, Nigeria and Mali. As of March 25, 2015, one year after the outbreak began, there have been 24,907 suspected and probable cases and 10,326 confirmed deaths (103). The causative agent in this current outbreak has been identified as the Zaire Ebolavirus, which marks not only the first time that this strain has been seen outside of Equatorial Africa, (10) but also the first time the virus has been found in densely populated urban areas, a fact that has contributed to its unprecedented spread (5).

Focus of thesis

There are many worthwhile aspects of the West African Ebola outbreak that will warrant examination and study in the months and years to come. Retrospective analysis of the behaviors of the initial case(s) will be analyzed and deconstructed in an effort to determine the zoonotic reservoir of Zaire Ebolavirus and the primary spillover event that started the outbreak (123). Scrutiny of how the cases have been clustered in terms of time and space will uncover the reasons behind the breadth and depth of human-to-human transmission. Sociological and Anthropological queries will concern the cultural factors, mores, political paradigms and infrastructure fissures that may have contributed to the unparalleled spread of the virus. The size of the outbreak has given the medical community and molecular biologists a unique opportunity to test experimental drugs, treatments and vaccines in the field, which has heretofore not been possible in an Ebola outbreak (62). They will closely examine the human immune response; the results can guide the direction of future research and drug development (30). Bioethicists will debate the merits and disadvantages of testing drugs in randomized clinical trials in the midst of a deadly outbreak. (11; 12; 13; 17) Questions surrounding who will and who will not receive the limited number of experimental anti-viral medications will be considered (14). Evidence from treating patients in the field can clarify best practices and frame future treatment protocols (55; 56; 57). Epidemiologists will calculate and study the Case Fatality Rate, Reproductive Number, statistically significant risk factors of death (139; 180). Analysis of this outbreak response will provide opportunities to improve future prevention and control.

For the purposes of this thesis, I will review the pathogenesis and molecular biology of the virus, immunological responses in humans to Ebola, transmission patterns, clinical manifestations of disease, the biological differences and markers that exist between survivors and those who succumb to Ebola infections; the suspected zoonotic reservoir; existing and novel treatments and vaccines; and finally the natural history of Ebolavirus outbreaks.

With respect to the 2014 Ebola outbreak, I will discuss the patterns of transmission and the cultural, political and human capital factors that may have contributed to the magnitude of the spread of the disease. However, my main concern rests with future programs and protocols that can be implemented to prevent an outbreak of this level in the future.

Methods

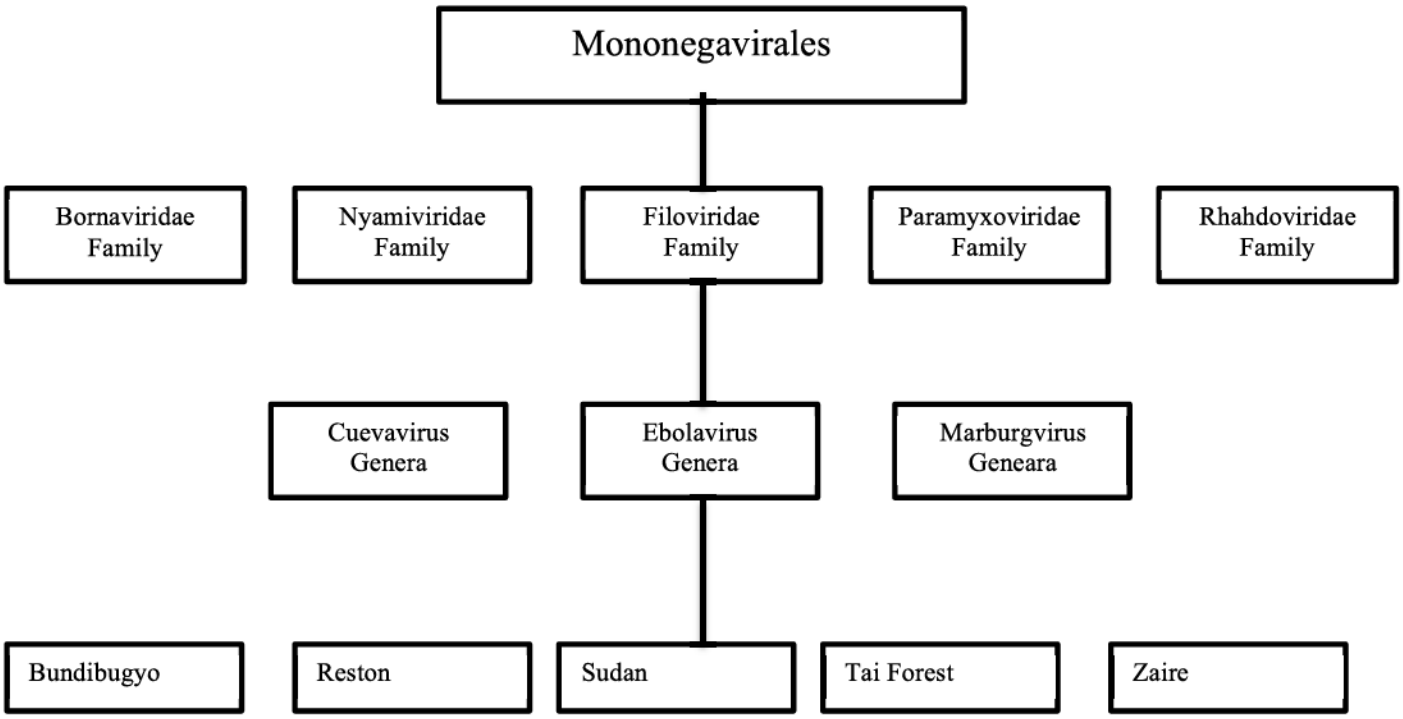
This thesis is a literature review of the history of the Ebola Virus and a summary of the 2014 Outbreak. Material and sources used with respect to past outbreaks, molecular biology, pathogenesis, immune responses, transmission, clinical presentation, current treatment protocols and the natural history of Ebola outbreaks came from peer-reviewed journals, all of which are listed in the Bibliography. Information on experimental vaccines and treatments was found from the manufacturers of the drugs themselves or from respected periodicals such as the New York Times and The Wall Street Journal. All data on the current Ebola epidemic in West Africa was culled primarily from the bi-weekly WHO Situation Reports, Doctors Without Borders Updates and UNMEER Situation Reports.

Filovirus Genera and Strains

The Ebola Virus genera belongs to the Filoviradae family of viruses in the Mononegavirales order (See Figure Three) (16). All Filoviruses encode their genome in a single stranded negative sense RNA and are known to cause disease in humans and non-human primates. In addition to Ebolavirus, the Filoviridae family also includes the Marburgvirus and Cuevavirus genera as members. While Marburg and Cuevaviruses only have one species or strain, Ebolavirus has five: Bundibugyo, Reston, Sudan, Tai Forest and Zaire. The Reston strain is non-pathogenic in humans, but does cause disease in monkeys and pigs.

Marburg virus was the first genera of the Filoviridae family to be discovered (104). In 1967, there were simultaneous outbreaks in Marburg, Germany; Frankfurt, Germany; and Belgrade, Yugoslavia. The epidemic began when laboratory workers in all three cities were initially exposed to the Marburg infected tissues and blood from African green monkeys that had been imported from Uganda. The virus spread via nosocomial transmission and to household contacts of lab workers. By the end of the outbreak, 31 people were infected and seven people died. Since 1967, there have been 12 cases and/or isolated outbreaks of the Marburgvirus, most of which have occurred in the central region of Africa, namely the nations of Gabon, Uganda, the DRC and South Sudan.

FIGURE THREE: TAXONOMIC SYSTEM MONONEGAVIRALES ORDER
Source: http://en.wikipedia.org/wiki/Mononegavirales



The ***Mononegavirales Order*** is the taxanomic home of neon-segmented, single stranded RNA viruses that has five different families and hundreds of different genera.

Bornaviridae contains the genera of virus that causes neurological syndrome in horses, although the disease is known to affect humans.

Paramyxoviridae is split into two sub-families: Paramyxovirinae and Pneumovirinae, both of which have several genera.

Subfamily Paramyxovirinae
Aquaparamyxovirus; Avulavirus, which causes Newcastle disease; Ferlavirus; Henipavirus, which include the Nipavirus and Hendravirus species; Morbillivirus, which causes Measles; Respirovirus, which includes the Human parainfluenza viruses 1 and 3 strains as well some of the viruses of the common cold; Rubulavirus, which causes Mumps

Subfamily Pneumovirinae
Pneumovirus includes the species that cause Human respiratory syncytial virus, Bovine respiratory syncytial virus, pneumonia virus of mice and canine pneumovirus and Metapneumovirus, which includes the species responsible for Avian pneumovirus, Human metapneumovirus.

Rhabdoviridae viruses infect a broad range of hosts throughout the animal and plant kingdoms. Animal rhabdoviruses infect insects, fish, and mammals, including humans. It has 10 different genera, including Ephemerovirus, which causes Bovine ephemeral fever; Lyssavirus; which causes Rabies; Novirhabdovirus, which causes Infectious hematopoietic necrosis; and Vesiculovirus, which causes Vesicular stomatitis Indiana Disease.

The Zaire and Sudan Ebolavirus strains were discovered in 1976 in Central Africa during two simultaneous outbreaks, both of which will be described in detail below.

A third Ebola Strain, Cote d'Ivoire (now known as the Tai Forest strain) was discovered in 1994 when an ethnologist was infected while performing a necropsy on a diseased chimpanzee. There was only one patient involved, the ethnologist, and she survived the infection. There have been no known cases involving this strain since. (97; 1)

The Bundibugyo strain was discovered in 2007 in the Bundibugyo district in Uganda. While the details involving the primary patient and the primary spillover event are scant, it is known that secondary transmissions occurred via close human contact. 149 people were infected in the outbreak and 37 people died, resulting in a Case Fatality Rate of 25%. (18). There has only been one other outbreak of the Bundibugyo recorded since, which occurred in 2012 in the Democratic Republic of Congo when 77 people were infected and 36 died (CFR of 47%) (105).

The fifth subtype (Reston) was discovered in 1989 in Reston, Virginia when scientists were investigating an outbreak of what was thought to be Simian Hemorrhagic Fever in Cynomolgus Macaques (187). Instead, they found that the monkeys were infected with a novel strain of Ebolavirus. It was suspected that the monkeys were exposed to this new strain of Ebolavirus while in transit to the United States from the Philippines. This strain has only been shown to cause disease in non-human primates; it has not exhibited pathogenic tendencies in humans.

The Cuevaviridae genera, and its sole member, Lloviuvirus, was discovered in 2002 when a team of scientists investigated a massive bat die-off in French, Spanish and

Portuguese caves (17). Initially suspecting pneumonia, the team instead discovered sequences of a unique member of the Filoviridae family in the spleen, liver and lung samples of dead M. schreibersii bats. They placed the novel virus in new genera Cuevaviridae, which is named for cueva, the Spanish word for cave. The strain itself, Lloviuvirus, was named after the Lloviu cave, where the virus was found. Interestingly, the virus sequences that were isolated in dead bats were missing in live bats of the same species, suggesting that Lloviuvirus infection may be pathogenic in bats. This would separate Lluoviuvirus from other Filoviridae species. Bats are thought to be the natural reservoir for the Ebolavirus and Marburgvirus strains and by definition they do not succumb to the disease even though they are infected and shed virus. While a bat natural reservoir had definitively been determined for Marburg virus, proving that bats are also the natural reservoir for Ebolavirus has proved elusive.

Sine the discovery of the Ebolavirus strain, there have been 13 occurrences of Zaire Ebolavirus strain, seven of Sudan Ebolavirus, two of the Bundibugyo and one of the Tai Forest. Of these, 19 can be considered outbreaks, not including the 2014 Outbreak in West Africa. See Table One. (18; 122).

Country	*Town*	*Cases*	*Deaths*	*Species*	*Year*
Uganda	Luwero District	6	3	*Sudan ebolavirus*	2012
Dem. Rep. of Congo	Isiro Health Zone	36	13	*Bundibugyo ebolavirus*	2012
Uganda	Kibaale District	11	4	*Sudan ebolavirus*	2012
Uganda	Luwero District	1	1	*Sudan ebolavirus*	2011
Dem. Rep. of Congo	Luebo	32	15	*Zaire ebolavirus*	2008
Uganda	Bundibugyo	149	37	*Bundibugyo ebolavirus*	2007
Dem. Rep. of Congo	Luebo	264	187	*Zaire ebolavirus*	2007
South Sudan	Yambio	17	7	*Sudan ebolavirus*	2004
Republic of Congo	Mbanza	35	29	*Zaire ebolavirus*	2003
Republic of Congo	Mbomo	143	128	*Zaire ebolavirus*	2002
Republic of Congo	Olloba	57	43	*Zaire ebolavirus*	2001
Gabon	Mekambo	65	53	*Zaire ebolavirus*	2001
Uganda	Gulu	425	224	*Sudan ebolavirus*	2000
South Africa	Johannesburg	2	1	*Zaire ebolavirus*	1996
Gabon	Booue	60	45	*Zaire ebolavirus*	1996
Gabon	Mayibout	37	21	*Zaire ebolavirus*	1996
Dem. Rep. of Congo	Kikwit	315	250	*Zaire ebolavirus*	1995
Côte d'Ivoire (Ivory Coast)	Tai Forest	1	0	*Taï Forest ebolavirus*	1994
Gabon	Mekouka	52	31	*Zaire ebolavirus*	1994
South Sudan	Nzara	34	22	*Sudan ebolavirus*	1979
Dem. Rep. of Congo	Tandala	1	1	*Zaire ebolavirus*	1977
Sudan	Nzara	284	151	*Sudan ebolavirus*	1976
Dem. Rep. of Congo	Yambuku	318	280	*Zaire ebolavirus*	1976

Source: http://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html

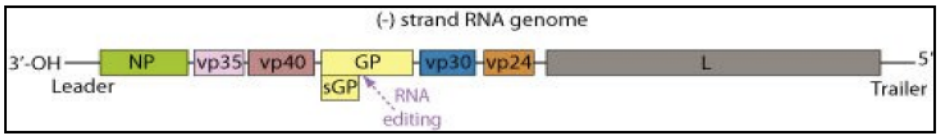
Table One (18; 122) Manifestations of Ebola Virus Disease in Africa.

Ebola Virus Molecular Biology

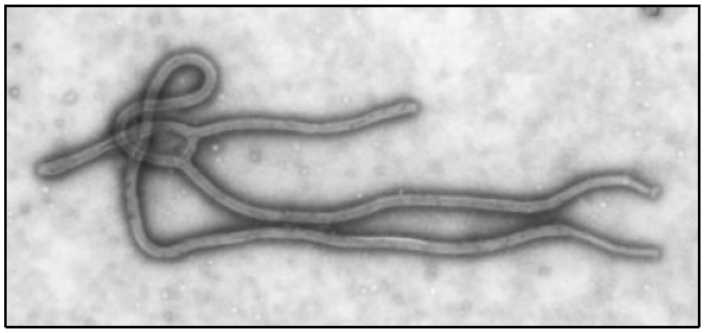
Ebolavirus is an enveloped, non-segmented virus that encodes its genome in a single stranded, negative sense RNA (16). It appears long and filamentous under the electron microscope, which helped give rise to the Filoviridae name. Ebola has a uniform diameter of 80 nm its length can reach 14000 nanometers. Its seven genes encode eight proteins, which are arranged in a linear order. Short nontranscribed regions are located at the extreme 3' and 5' ends, called the leader and the trailer, respectively. The structural proteins are arranged as follows (See Figure Four): nucleoprotein (NP), virion protein (VP) 35, VP 40, Glycoprotein (GP), VP 30, VP 24, and an RNA dependent polymerase (L). All encode for one structural protein, with the exception of GP, which also produces a soluble protein, sGP, which is secreted into the bloodstream from infected cells. This soluble glycoprotein is distinctive to the Ebolavirus genera, as no other virus in the Mononegavirales order produces a soluble protein from its genome.

Each of the proteins in the Ebola genome multitask, making Ebola incredibly efficient. VP24, VP35 and NP work together to form nucleocapsid structures (23); NP and VP30 are responsible for capsid assembly and binding viral RNA (19); VP30, VP35, NP and L are involved in transcription and replication of the genome (22); L, VP40 and VP35 mediate assembly of new virions (22); VP40 and VP24 direct virus budding (19). The genes also functional individually: VP35 and VP24 act as interferon antagonists (16), which create an environment conducive for unrestricted viral multiplication; V4P40 is the main protein involved in particle formation and maintaining structural integrity of the virion (19; 16; 23) and GP mediates entry into host cells (19). The role of sGP is unknown, but it is thought that it might act as a decoy for antibody surveillance in the

blood, distracting the immune system while the real virus infects cells and replicates (20; 21). The genome of the virus and its RNA are encapsulated inside the lipid bilayer envelope, which originates from the host cell membrane that protects the viral genome and facilitates entry into host cells (32).



Source: https://www.askscientific.com/ebola-virus-life-cycle-and-pathogenicity-in-humans/



Source: http://www.riskscience.umich.edu/still-ebola-role-technology-global-health/

Figure Four: Cartoon of the Ebolavirus Genome (top) and an Electron micrograph (bottom) of the virus.

GP, the trimeric-spiked main surface protein embedded in the bilayer of the virus, is responsible for binding to host cells and mediating fusion between the viral envelope and the host cell membrane (21). It is formed by two parts: GP1 and GP2 (16). GP1 forms the trimeric spikes that are visible on the exterior of an Ebolavirus (see Figure Five and Six) and are heavily glycosylated. The receptor-binding site on GP1 that is imperative for attachment and entry into host cells, and the actual target of neutralizing

antibody, is hidden underneath the glycan caps. These binding sites are only revealed when GP1 is cleaved after it enters the endosomal compartment of the host cell (22). GP2 is tasked with fusing with host cell membranes and initiating entry into the cytoplasm of the cell. The structure of GP, and the sequestering of the antibody binding site, ensures that antibody surveillance of the host immune system is not the same as antibody receptor binding, a trait that is thought to contribute to immune system evasion (23).

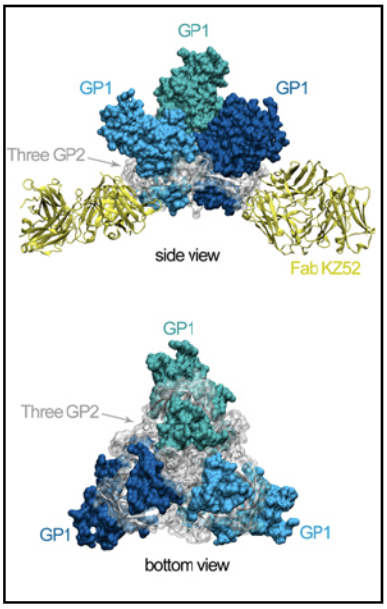
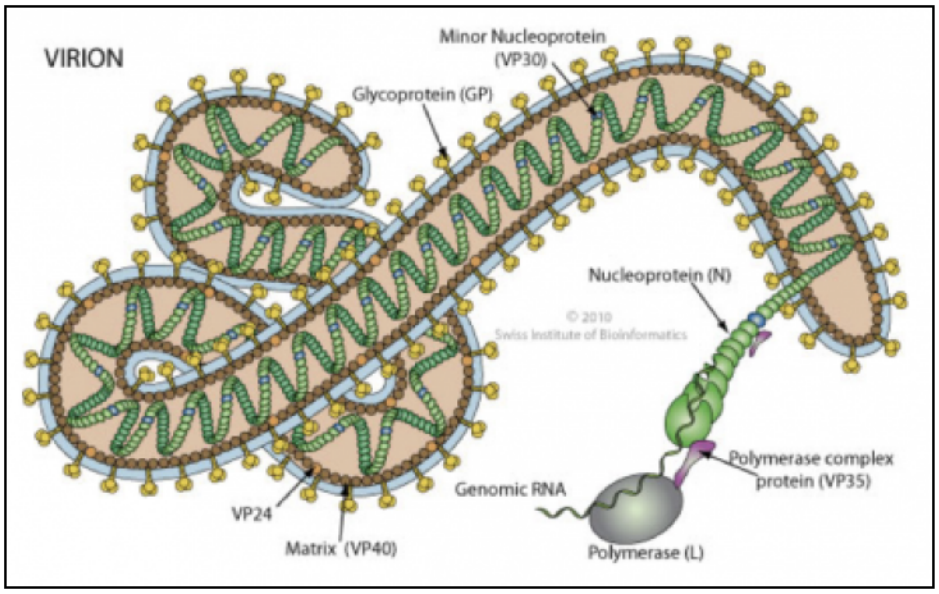


Figure Five: The three GP1 subunits (blue and green) are tied together by three GP2 subunits (white). GP1 mediates attachment between the receptor binding sites that are located underneath GP1 and host cell endosomal membranes. GP2 allows fusions of the viral membrane with the host cell.

Source: https://www-ssrl.slac.stanford.edu/research/highlights_archive/ebolavirus.html



Source: https://www.askscientific.com/ebola-virus-life-cycle-and-pathogenicity-in-humans/

Figure Six: The Ebola Virion

Ebola Pathogenesis

Scientists have not yet determined the essential surface protein on host cells that Ebolavirus targets and attaches to, but it is known that dendritic cells are one of the first cells to be attacked in an Ebola infection (26). It has been speculated that Ebola gains entry into cells by producing an increased amount of phosphatidylserine, a lipid that is exposed when cells are primed for apoptosis (22). By expressing phosphatidylserine, Ebola tricks dendritic cells into thinking that the virus is in fact debris that needs to be engulfed and destroyed, thereby essentially inviting itself into the dendritic cell endosome. Vaccinia virus also uses this mode of apoptotic mimicry; it is thought to be a survival mechanism for larger viruses, such as Ebola and Vaccina, because it would be difficult for them to enter cells via more traditional routes (106).

Once a cell is targeted by Ebolavirus, the GP spikes bind to the surface of that cell and the virus gets taken up into the endosome by macropinocytosis (22). However, Ebola needs to gain access to the cytoplasm before it can replicate. In order for the virus to escape the endosomal compartment, two cysteine proteases: cathepsin B and cathepsin L cleave GP into two separate molecules: GP1, a receptor binding subunit and GP2, a membrane fusion subunit (21). Although viruses normally avoid cysteine proteases because they are known to break down viral particles, Ebola needs these enzymes to jettison the heavily glycosylated caps that form the GP trimer (22; 27; 28). Once cleaved, the receptor-binding fragment (18kD N-Terminal Fragment) that resides on the underside of GP1 is exposed (27). This fragment binds to Niemann Pick C1 (NPC1), a protein that dwells in endosomal membranes (NPC1 normally traffics intracellular cholesterol) (22). NPC1 acts as a receptor for Ebolavirus and expedites viral entry (28). In fact, without this

receptor, Ebola is stuck in the endosome and is rendered non-functional, and for this reason is currently being studied as a possible anti-viral drug target.

NPC1-GP1 binding is imperative for viral escape from the endosome and entry into the cytoplasm of the cell. While GP1 binds to NPC1, GP2 is responsible for mediating the fusion of the virus to the endosomal membrane (23). The virus is then taken up into the cytoplasm of the cell where the genome is uncoated, transcribed into mRNA, replicated and assembled. New viruses are formed, released and available to target new cells.

As mentioned above, Ebola's early and preferred sites of viral replication are dendritic cells, the primary antigen presenting cells of the innate immune system (16). One of the main functions of any antigen presenting cell is to alert the adaptive immune system of viral invasion by capturing antigen and presenting it to naïve TCells (in the context of Class I MHC) that reside in the lymph nodes. Dendritic cells also are responsible for secreting prostimulatory cytokines that induce cellular and humoral adaptive immune responses that can clear an infection. Ebola-infected dendritic cells never mature or secrete the cytokines necessary to upregulate MHC Class I to the cell surface and antigen can't be presented to TCells in the lymph node (233). As a result, neither cellular nor humoral responses will be activated (233; 26). By infecting and disabling dendritic cells, Ebola eliminates the critical link between innate and adaptive immune systems.

Infected dendritic cells are also tasked with releasing interferon, a type of cytokine that slows down viral replication, which gives the immune system time to mount an adaptive immune response (233). However, one of the hallmarks of an Ebola infection

is its ability to prevent the activation of interferon. Specifically, VP24 and VP35 serve as interferon antagonists that leave the immune system highly compromised and unable to control viral replication (16; 26; 29; 30).

The second target cells of Ebola are monocytes and macrophages, also cells of the innate immune system (16; 26). Their main responsibilities are to phagocytize cellular debris and present antigen to naïve TCells, much like dendritic cells. Under normal circumstances, infected macrophages and monocytes release inflammatory cytokines upon encountering an antigen, such as TNF, IL1, IL2, IL6, IL15, IL8, and MIP1 and nitric oxide (29). TNF, IL6, IL8 and IL12 are inflammatory cytokines that are responsible for many of the symptoms that are associated with an illness, such as fever and lethargy. They are also responsible for vascular permeability, which allows lymphocytes access to the site of infection. MIP1 and MCP1 are tasked with recruiting more monocytes and macrophages to fight off pathogens (233).

Towards the tail end of an infection a regulatory process is activated by IL10, an anti-inflammatory cytokine. IL10 suppresses the production of inflammatory cytokines and allows the body to return to its normal state (233). However, during an Ebola infection, the inflammatory process is never regulated and inflammation operates in a continuous loop. Infected macrophages travel to the lymph nodes; they express cytokines that increase inflammation and growth stimulation chemokines that attract more monocytes and macrophages to the site of infection; these new monocytes and macrophages become infected themselves; they in turn express more cytokines, which increases inflammation; and so on and so on (30).

While IL10 has been detected in patients who have fatal Ebola infections, it could be that not enough is produced to overcome cytokine storm that causes much of the pathogenesis associated with the disease. Unregulated inflammation and viral replication are responsible for coagulation abnormalities; hypotension (the result of hepatocellular damage and high nitric oxide levels); increased vascular permeability, including damage to endothelial cells (generally late in an infection), vascular collapse, severe vomiting, diarrhea, hypovolemic shock and organ failure. (16; 29; 31) Ebola patients also experience large loss of lymphocytes, known as bystander lymphocytes apoptosis. While lymphoid tissues are targets for viral invasion, the lymphocytes themselves are not. The apoptosis is correlated with an increase of Fas/FasL and TNF-induced TRAIL ligands, but the mechanisms underlying the cause of the apoptosis are not well known. It is thought that dendritic cell dysfunction or an overproduction of nitric oxide from infected macrophages might play a role in stimulating the large die-off of lymphocytes (29; 31; 16; 30; 38).

Necrosis of the liver, while not fatal in and of itself, results in decreased synthesis of coagulation factors, which contribute to hemorrhagic symptoms and are consistent with disseminated intravascular coagulation (31; 16). It also has been speculated that tissue factors released from infected macrophages and monocytes may be responsible for coagulation disorders (16).

Immune Response to Ebola Infections

There is considerable debate in the scientific community regarding the adaptive immune response in Ebola patients. In particular, a consensus has not been reached about which arm of the adaptive system is more essential: TCell activation or antibody production. Part of the problem in coming to an agreement is the dearth of Ebola studies on human subjects. Ebola outbreaks occur unexpectedly and infrequently and when they do, patients oftentimes die too quickly to obtain measurable samples (42; 30). Furthermore, the lethality of the virus leaves very few options for cellular experiments or autopsy because Ebola must be tested and examined in a BSL4 laboratory. There are fewer than 50 of these labs in the world and none that exist in Ebola endemic regions (sources: http://fas.org/programs/bio/biosafetylevels.html and https://www.google.com/fusiontables/DataSource?snapid=S567513UnBn). As a result, most of the understanding with respect to how the adaptive immune system functions during an Ebola infection is extrapolated from mouse, guinea pig and non-human primate models. Most of these experiments are done in the context of measuring immune responses in a variety of vaccine platforms and the results are at times contradictory. For example, some mouse models were able to show that protection from lethal Ebola challenge was defined by a robust CD8+ TCell response and that CD4+ TCells were not required for eVLP-mediated protection (32; 33; 34; 30) while other studies in non-human primates showed the opposite effect (35; 30). Likewise, the research on the necessity of a humoral response in mouse and non-human primate models is contradictory as well (35; 30; 36).

Despite the pathogenicity of the Ebola virus, there have been studies done on human blood samples that have elucidated the differences in the immune responses between patients who die from an Ebola infection and those who live. One study was done on a subset of patients from the Mayibout and Booue outbreaks in the Gabon in 1996 (37). A longitudinal analysis was performed on blood samples that were taken from a group of fatal cases and survivors over the course of their illness and during the recovery period of survivors. A control group of healthy people who were not infected with the virus was also included in the analysis. The results indicated that fatal outcomes were associated with a suboptimal humoral response defined by indiscernible IgM and no detection of IgG production whatsoever. The release of Interferon-gamma in the early days of infection in fatal cases indicates that the immune system attempts to mount an TCell response but these early efforts are followed by the complete disappearance of TCell activity (as measured by TCell related mRNA) and extensive lymphocyte apoptosis during the last five days infection. Although viral titers were relatively equal between fatal cases and survivors on Day 2 of the disease, by Day 4 fatal cases had viral titers that were up to 200% higher than survivors.

Patients who survived an Ebola infection mounted early IgM antibodies and Ebola specific IgG directed at VP 25, VP40 and NP. While survivors did not mount a CD8+ response during the symptomatic phase of the disease, increasing levels of Fas Fas L and perforin during the recovery phase indicate that a cytotoxic TCell response corresponds with viral clearance from the blood. While both humoral and cellular responses are important for clearing an infection, the severely impaired and non-

functional antibody responses in fatal cases support the theory that the humoral activity is imperative to control virus replication.

A cross sectional study was done using blood samples taken from 42 non-survivors and 14 survivors of the Gabon and Democratic Republic of Congo outbreaks from 1996 and 2003(38). Those who cleared the infection were able to regulate the inflammatory cytokine storm brought on by infected macrophages and monocytes; did not experience bystander lymphocyte apoptosis; and mounted early humoral and cellular responses, including tightly regulated activation of cytotoxic TCells. Fatal cases experienced cytokine levels that were five – 1000 times greater than those found in healthy people and peaked two days before death.

Immune events that occur early in the infection can determine whether or not a person will be able to control viral replication or if the infection will result in death (29). A fatal case of Ebola will successfully suppress the innate and adaptive immune responses by infecting and disabling dendritic cells. Infected macrophages secret inflammatory cytokines that are never regulated and results in prolonged cytokine secretion (38). VP35 and VP24 suppress interferon activation, allowing the virus to proliferate and spread throughout the body via the circulatory system. Although TCell activation is attempted, it is quickly disabled by down-regulation of Type One interferon (38). Increased lymphocyte apoptosis results in increasing viral loads; patients who fail to recover also have virtually no viral antigen specific antibodies (29). By the end of a fatal infection, patients suffer from chronic inflammation and high viral titers that manifest in systemic organ failure, impairment of the vascular system, hypovolemic shock and death (16; 29).

Although there are clear immune response disparities between survivors and fatalities, it has been difficult for scientists to understand why exactly some people can clear the infection and some cannot. It has been suggested that the Ebolavirus is not able to replicate in people who are deficient in the NPC1 gene that is imperative for viral entry into the cell cytoplasm (28) (NPC1 deficiency results in Niemann-Pick disease, a recessive disorder that causes accumulation of cholesterol in the endosome of cells).

There may be confounding factors as well such as underlying/pre-existing health conditions, co-infections and general overall health prior to exposure to Ebola (30). Also, individuals who seek and obtain proper care as soon as symptoms present themselves, and before viral load and inflammation become uncontrolled, invariably have more positive outcomes. The mode of infection may be a factor. In the inaugural Zaire Ebolavirus outbreak, those who were infected through the use of contaminated needles had a 100% fatality rate, while the overall case fatality rate for the infections transmitted by close contact is around 70% - 90% (16; 11).

Ebola Virus Transmission, Clinical Presentation, and Asymptomatic Cases

Transmission

The Ebola virus can only be transmitted when a susceptible individual comes into direct contact with the bodily fluids of an infected and symptomatic Ebola patient (39; 41). These bodily fluids include: vomitus, feces, blood, saliva, tears, breast milk, and semen. Breast milk and semen were found to be culture positive after Ebolavirus had already cleared from the blood and up to 40 days post disease onset (40). The virus contained in these fluids enters the uninfected host through breaks in mucosal surfaces or abrasions in the epidermis (5; 16).

The route of transmission that carries the most risk is household transmission, which generally occurs when a family member or friend cares for an Ebola patient and is exposed to the virus through close personal contact. Data from the first Sudan Ebolavirus outbreak in 1976 indicated that persons who provided nursing care to sick family members had a 5.1 fold increased risk of infection (95). A study of patients in the Kikwit outbreak in 1996 showed that direct physical contact with an infected person during the clinically apparent phase of illness was the most important risk factor for household transmission (96).

Nosocomial transmission can occur when health care workers are exposed to the bodily fluids of infected patients. Ideally, doctors and nurses should protect themselves by wearing personal protective equipment (PPE) with full body coverage. However if the strict donning, doffing and decontamination protocols are not followed, there is a risk of viral transmission and self-contamination. Of particular concern is the removal of PPE after caring for patients. Even if the protective gear is put on properly and no exposure to

virally infected bodily fluids occurs during the course of care, a health care worker can still become infected if there is a breach in doffing protocols (121). Ebola viruses can live on inanimate objects and fomites for up to a few hours (or longer in ideal conditions), (39; 40) therefore in order to prevent exposure to the virus it is imperative that the removal of PPE and proper decontamination procedures are followed in a systematic way and under supervision.

The lack of PPE and the unfamiliarity with its proper use is not a problem that is peculiar to West Africa. Hospitals in the developed world also ran into nosocomial challenges while treating Ebola patients. A nurse in Spain also contracted the disease when she touched her face with the gloves she wore while treating a Spanish missionary priest (42) After Thomas Eric Duncan was admitted into Dallas Presbyterian Hospital with Ebola in the September 2014, two nurses who cared for him were infected with the virus. It is thought the lack of appropriate protective gear; improper training; and lax disinfecting procedures were the reasons behind the transmission of the virus (43).

In past outbreaks, nosocomial transmission has accounted for a significant proportion of cases. In the first outbreak in Zaire, the single greatest risk factor for contracting Ebola, especially during the early part of the epidemic, was receiving an injection at the Yambuku Mission Hospital (which was the focal point of the outbreak). Furthermore, 11 out of 17 of the Mission Hospital staff died and the hospital had to close (52). During the 1976 Sudanese outbreak, Maridi Hospital was the amplifying source of the epidemic where 46% of the cases hospitalized (93). A quarter of the 315 cases in the 1995 Ebola outbreak in Kikwit were among doctors and nurses, all of whom cared for Ebola patients without protective gear (45). During the 2007 Ebola outbreak in

Bundibugyo, Uganda, 14 healthcare workers were infected before implementation of standard barrier practices. After implementation of the precautions there were not any nosocomial cases reported (45).

People in Africa are also at risk of exposure to the virus when they participate in traditional funeral practices where is it common for mourners to wash, kiss and touch corpses. Unlike other viruses, Ebola remains pathogenic in the blood and bodily fluids of a deceased patient and those who handle or touch the bodies are at risk of being exposed to the virus (2; 16; 5; 39). The funeral rite can last for weeks as the deceased are often transported back to their home communities for the burial. In addition, family members and friends travel significant distances to attend funerals and then return home, enabling the virus to spread across borders (97).

While it has been suggested that Ebola may be transmitted via an airborne route through the inhalation of aerosols, there isn't much evidence to support this. Airborne transmission of a virus requires inhalation of an infectious dose of that virus in droplet nuclei form. These small infectious particles are able to penetrate the deepest tissues of the lung, where the virus will attach to the endothelial cells of the respiratory tract and become pathogenic.

In the case of Ebola, the target cells of the Ebolavirus do not reside in the epithelial cells of the bronchial tubes, respiratory tract or lung, but rather in the cells of the innate immune system, such as dendritic cells, macrophages, monocytes, and eventually the vascular system. Research that has been conducted thus far on the pathogenesis of Ebola has not shown that the cells of the respiratory tract become

infected and very few patients show respiratory symptoms such as coughing and wheezing (120).

Clinical Presentation of Disease (46)

The clinical symptoms of an Ebola infection follow a common pattern. After *initial virus exposure*, there is a two-21 day incubation period (mean of five-seven days) during which a patient has a pre-clinical infection and is not considered contagious and cannot transmit the virus to a non-infected person (16; 39). After the incubation period is over and Ebola viral load reaches a certain threshold, there is abrupt onset of symptoms after which point a person is contagious and able to transmit the virus.

Symptom manifestation can be divided into three distinct groups. In the early febrile phase, zero-three days post symptom onset, patients experience fever, malaise, fatigue, body aches and anorexia; all non-specific symptoms that can be misdiagnosed or confused with malaria, typhoid, cholera or influenza.

In the second gastrointenstinal phase, generally three to 10 days post symptom onset, fever persists as gastrointestinal symptoms begin to manifest with patients experiencing nausea, vomiting and diarrhea. In some patients, the fluid loss is of the magnitude of cholera patients: up to five (possibly 10) liters a day. It is during this phase that hemorrhagic symptoms will appear which includes petechiae, ecchymoses, oozing and bleeding from venipuncture sites, mucosal hemorrhages and macropapular rashes (16).

In the third phase, seven to 16 days after symptom onset, patients diverge into one of two categories: those who succumb to the infection and those who will survive. In

those cases that will be fatal, there is profound fluid loss due to chronic diarrhea and vomiting that results in electrolyte depletion. The body goes into circulatory collapse, hypovolemic shock, and systematic organ failure, most notably metabolic acidosis and a failure to produce urine (16). During this phase patients can also suffer from hyponatraemia, which can cause brain swelling with raised intracranial pressure (107). Patients also tend to lose consciousness or fall into a coma and experience rapid breathing before death. In patients who will survive, symptoms begin to improve during this phase, and most patients who survive to day 13 ultimately live (16; 46).

Asymptomatic Cases of Ebola

While most patients infected with Ebolavirus exhibit severe symptoms, there have been documented cases of patients who are clearly infected with the virus (as measured by circulating anti-Ebola antibodies and a positive RT-PCR for Ebola RNA fragments), yet remain asymptomatic throughout the course of the disease (47; 48; 49; 50). It is assumed that these individuals are most likely not infectious, and it is likewise assumed that their exposure confers protective immunity, despite the fact that they did not present symptoms (50; 46).

Retrospective serological surveys done after the inaugural Ebola outbreak in Sudan in 1976 showed that 19% of contacts of persons with the disease had anti-Ebola antibodies even though they never became ill themselves (51). During the 1976 Zaire Ebolavirus outbreak, less than 2.5% of people who had contact with fatal cases experienced subclinical infections (52). Furthermore, serological surveys conducted in 1977 in the Tandala region of Zaire showed that 79 out of 1096 people (7%) tested were found to have antibodies to Ebola although they gave no history of severe disease (51).

More recently, after the Kikwit outbreak in the Democratic Republic of Congo in 1996, samples taken from 152 contacts of confirmed Ebola patients showed that five of them (3.2%) were IgM and IgG positive even though there was not morbidity associated with their infection (53).

In Northeastern Gabon there were three Zaire Ebola outbreaks between 1994 and 1996 (47). Nine hundred and seventy nine (979) people from the region were serologically tested (taken from a study population of 2533) in an attempt to ascertain the level asymptomatic cases from those outbreaks. The results showed that 14 of the 979 were seropositive for IgM and IgG anti-Ebola antibodies. Of these 14, four were listed as previous cases in official documents from the February 1996 outbreak and each one of them had clinical disease and typical Ebola-like symptoms. The remaining ten seropositive people were not listed as patients in any outbreak and did not report having had Ebola-like symptoms (51).

In another study of asymptomatic patients from the Gabon in 1996, investigators sampled 24 contacts of diagnosed Ebola patients (48; 49) (it is unclear how investigators came to study these particular 24 people or why they were chosen in the first place. It is likewise unknown what the underlying health conditions were of the 24 people). Each contact was prospectively studied to measure immune responses and disease progression. They all shared a household with laboratory confirmed Ebola patients and administered care to them without any protective equipment, even rudimentary prophylaxis such as gloves. Although they were directly exposed to the feces, vomit, sweat and blood of non-fatal and fatal Ebola patients, they did not develop symptoms (49).

Samples from the 24 individuals were taken on four occasions over a one-month period, starting with one week after initial exposure to the virus. The first samples that were taken did not detect antibody, indicating that they were Ebola naïve and had not previously mounted an immune response. Two to three weeks after exposure, 11 of the 24 patients produced measureable Ebola specific IgM and IgG response to Ebola antigens. IgM antibody was detected 15 – 18 days post viral exposure, followed by Ebolavirus specific IgG2 and IgG3 antibody reactive to NP and VP40 approximately one week after that (48). Antibody production in asymptomatic patients was delayed in comparison to antibody production in symptomatic patients (53).

Although circulating Ebola antigen was never detected, at day seven to day 21 post exposure, Ebola RNA was detected in seven out of the 11 antibody positive asymptomatic individuals via nested RT-PCR. Furthermore, the RNA fragments were only found in the peripheral blood mononuclear cells, indicating a low viral load, which is consistent with the lack of circulating antigen (48).

All told, 46% of close contacts of Ebola patients in this study had replicative Ebola infection and did not present any symptoms of the disease (49). While the number of asymptomatic patients uncovered in the studies reviewed here are very low, they nonetheless establish that it is possible for people to have exposure to the Ebolavirus, develop an infection that provokes an immune response, yet never present symptoms. The authors do not hypothesize that this percentage could be applied to any or all Ebola outbreaks, rather they only reported on what was found in this individual investigation. In absence of further studies, it is difficult, if not impossible, to assume that the same percentage of asymptomatic individuals can be found in any given Ebola outbreak.

There have also been known cases of Ebola infected patients who do have symptoms, but they are very mild. In the 1976 outbreaks, WHO teams noted that there was a continuum of symptoms that ranged from mild to rapidly fatal (52). In the 2007 outbreak in the Democratic Republic of Congo, it is thought that the index patient, a 42-year-old man, contracted the virus after handling bats he purchased in a market. His only symptoms were a low-grade fever and headache, and never transmitted the virus to his wife, with whom he is assumed to have had close contact. However, his daughter became ill and died during a time frame that was consistent with the Ebola incubation period, leading investigators to conclude that her father infected her. An investigation into the lifestyle patterns of that family suggested that while the father walked from town to his home village, a trip of three to four hours, he carried his daughter on his back. It was speculated that the daughter could have become infected through exposure to her father's sweat (39; 54).

Treatment of Ebola

As was discussed above, Ebola survivors have a very different immune response to the virus than those who die from the disease. Survivors mount an early innate response that is marked by cytokine regulation as well as an adaptive response that is defined by anti-Ebola antibody production and cytotoxic TCell activity. Although the scientific community has been able to establish that there are indeed differences in immune responses, the reasons why there are differences have remained elusive. Potential confounders and genetic differences have been discussed above. Disparities in the qualitative and quantitative measures of care also have been considered a defining factor in determining patient outcomes (55; 107) Several reports from the field of the West African outbreak have provided more details as to what kind of treatment in particular is thought to contribute to patient survival. Specifically, patients who are treated with aggressive rehydration therapies under adequate medical supervision have a greater chance of survival (56; 57; 58). Although oral and intravenous rehydration therapies have been used in past outbreaks: intravenous fluids were first used in the 1976 outbreak in Zaire to treat three nuns. In Kikwit in 1995, rehydration therapies were used in the last few weeks of the outbreak in approximately 25 patients (60). However, their effectiveness has not been rigorously evaluated (55).

Aggressive rehydration therapy was thought to have been a factor in the treatment of two Ebola patients who were treated at Emory University Hospital in July – August 2014 (59). Patient One began treatment in Atlanta on Day 10 of his illness; Patient Two began her treatment on Day 15. Both patients were hypovolemic upon presentation; had low potassium, calcium and sodium measurements; and both showed signs of liver

dysfunction, manifestations that are all known significant risk factors for death. Patient One had more severe symptoms: persistent rash, vomiting of blood and diarrheal output of 2-4 liters a day, while Patient Two didn't experience nausea or vomiting and remained afebrile throughout the course of her illness.

Upon admission to Emory, both patients received aggressive fluid and electrolyte replacement with an emphasis on potassium and calcium replacement. At the beginning of his illness in Africa, Patient One received intravenous Ringers Solution and was able to drink Tang and Gatorade, despite anorexia. Patient Two was well enough in Africa to drink oral rehydration fluids from the onset of her symptoms.

Both patients received three doses of ZMAPP in the context of their treatment and Patient One also received one unit of convalescent whole blood from a patient who recovered from Ebola. Because both patients received different layers of treatment throughout their illness, it is difficult to isolate which treatment in particular may have had the largest impact on recovery. However, doctors who treated both patients, and investigators who reported on the protocols used at Emory, believe that rehydration therapies, with an emphasis on calcium and potassium replacement, had significant value in the recovery of these two patients.

Under normal circumstances, intravenous fluid therapy and electrolyte replacement could assuage dehydration, but it is difficult, if not impossible, to extend this type of care in an Ebola hot zone considering the number of patients, the dearth of health care workers and the limited time in, and the cumbersome nature of, personal protective equipment (55; 56; 61; 107).

It is important to consider that the Emory patients were treated under ideal conditions: they were in an internationally known hospital with a 24 hour staff dedicated exclusively to monitoring their progress and maintaining fluid and electrolyte levels. While this type of intense care does not exist in West Africa, rehydration therapies have nonetheless improved outcomes in Ebola patients there. In Nigeria, only 40% of patients in the recent outbreak died, and intense rehydration therapy was credited with the high survival rates. Some patients in Nigeria were drinking up to five or six liters of Oral Rehydration Solution a day, at times forcing themselves to do so despite overwhelming nausea, weakness and lethargy (56; 57). One patient reported that it was difficult for her to even wrap her fingers around her cup, let alone lift it to her mouth to drink. Although this data is anecdotal in nature, and cannot be proven scientifically, Nigerian doctors believe that focusing on rehydration as the main component of patient management made a difference in patient outcomes.

A more systematic study was conducted on 37 laboratory confirmed Ebola cases in Conakry, Guinea from March 25 – April 26 (58). All 37 patients were treated in an MSF-run Ebola Treatment Center and were admitted, on average, five days after symptom onset. Most presented with symptoms typical of an Ebola infection: fever, vomiting, diarrhea, lack of appetite and lethargy. Very few of the patients had known co-infections or conditions, and a regression analysis revealed that age was the only statistically significant predictor of death (Relative Risk of death for those over 40 compared to those under 40 == 3.49; pvalue = .0007). Investigators did not include the type of treatment received into the model, so it is impossible to know how significant the different regimes were in preventing death. However, 99% of patients (N=36) received

Oral Rehydration Therapy and 77% of those (N=28) were also given intravenous fluids. The Case Fatality Rate for this group of patients was 40%. The authors of the study concluded that the use of oral and intravenous fluids and electrolyte replacement did improve survival rates in this Ebola Treatment Center above all other kinds of treatments that were given.

By way of comparison, the Case Fatality Rate at the very beginning of the outbreak in Guinea was 86% among confirmed cases and 71% among clinically suspected cases. It is suspected that most of those early cases were misdiagnosed and/or did not receive medical care specific for Ebola, if they received care at all (1). Therefore comparing Case Fatality Rates from the beginning of the outbreak to the Case Fatality Rates reported in this study of 37 patients at an MSF-run Ebola Treatment Center might not be a fair comparison. At best, it might be a comparison between Case Fatality Rates of those who received no medical treatment at all to those who received any kind of medical treatment.

Another Ebola Treatment Center in West Africa likewise concluded that rehydration therapy ameliorated the consequences of hypovolemic shock and contributed to the survival of Ebola patients (46). Doctors from the ELWA-3 Ebola treatment center in Monrovia, Liberia put a priority on rehydration therapies and implemented a systematic way of categorizing patients according to their rehydration needs upon presentation: 1. Hypovolemic, not in shock, and *able* to provide self-care; 2. Hypovolemic, not in shock, but *unable* to provide self-care; and 3. in shock with evidence of organ failure whose outcome would not be altered by any available medical intervention. It was observed that early rehydration interventions, whether administered

orally or intravenously, controlled symptoms, mitigated massive gastrointestinal losses (up to five – ten liters a day), limited the life-threatening consequences of hypovolemic shock and increased the chance of recovery (107).

However, the success of these treatments is only as good as a doctor's ability to implement them. Routine use of intravenous therapy in ELWA-3 was hindered by the number of doctors and nurses available to care for patients (this study cited a ratio of 1 doctor for 30-50 patients) and the limited time that health care staff was able to be in personal protective equipment (each doctor was limited to 60 minutes three times a day in protective gear, which equaled one – two minutes per patient per day). Indeed, this gap in quantitative measures of care seems to be the primary deterrent to including aggressive hydration therapies in the treatment of patients.

It has not been proven statistically that the use of rehydration therapies, oral or intravenously, have an impact on reducing case fatality rates and improving patient outcomes. All that we have are narratives from previous outbreaks and from the field in West Africa. Nonetheless, it is believed that many Ebola patients are dying without adequate fluid resuscitation and that this 'unmet standard of care' (61) is being wholly underused (56; 107). Doctors in the field in West Africa and those who have been studying this outbreak endorse a focus on immediate and consistent rehydration as a significant way to save the lives of Ebola patients (107).

Experimental Treatments for Ebola: Vaccines and Anti-Viral Therapies

Although there are no vaccines and anti-viral medications approved to treat Ebola patients, there are several new drugs under development, some of which are currently in clinical trials.

Blood Product from Convalescent Patients – This type of therapy involves transfusing blood products from Ebola survivors into currently infected Ebola patients (62; 63; 64). The hope is that neutralizing antibodies contained in survivor blood will prime the immune system of the infected patient and enhance the ability of the recipient to clear the virus (64; 66). This treatment has had mixed results in non-human primate experiments. A 2007 study showed that neutralizing human monoclonal antibody, KZ52, an antibody that was derived from a survivor of the Kikwit outbreak, not only failed to protect macaques against challenge with Ebola virus but also had a minimal effect on the explosive viral replication following infection (64). However, it did show potential neutralizing activity in cell culture and small animal models.

On the other hand, during the 1995 outbreak in Kikwit, eight patients were given whole blood transfusions from Ebola survivors of that same outbreak. Seven of the patients survived, however they were given the treatment late in the progression of their disease and it is thought that they most likely would have survived anyway (65; 66). In the Yambuku outbreak in 1976, 13 Ebola survivors donated plasma, and a laboratory technician received one of the units and survived (108). Likewise, in the 2014 outbreak, Dr. Ken Brantley was given a transfusion from an Ebola survivor in Africa and he in turn donated his own blood to three patients in the United States (66). All four of these

patients (Dr. Brantley and the three patients who received his blood) were also receiving concurrent aggressive therapies, which makes it difficult to ascertain how effective the transfusions were.

There are at least three clinical trials in the offing that will attempt to evaluate the effectiveness of blood therapies. In October 2014 it was announced that the European Commission was giving $3.7 million to fund a clinical coordinated by the Institute of Tropical Medicine in Antwerp, Belgium and run by MSF (109; 110; 66). The randomized trials are currently being held in Guinea (as of April 2005) where 200-300 patients will be given blood plasma from recovered patients (119). While there is not a control group per se, patient outcomes will be compared against outcomes of patients who did not receive transfers because a donor could not be matched.

The Bill and Melinda Gates Foundation also earmarked $5.7 million to fund another clinical trial in Liberia (63; 109) that is being run by Clinical RM, a US medical research organization (110). The trial protocol delineates that 70 participants will receive plasma (119) from survivors at the ELWA2 hospital in Monrovia (109) in three 200ml doses over the course of four days. The control group, comprised of patients who are not eligible to receive the plasma due to incompatibilities with the donor pool, (109) will receive the same standard of care regime as the treatment group, which is defined as intravenous fluid treatment and the consistent monitoring of vital signs, electrolyte levels and blood pressure (63). Post treatment measurements of viral load will be tracked pre and post transfer and both groups will be followed until either recovery or death. A concern in this trial in February 2015 was the dearth of patients (less than five cases a week); the fact that some patients are ineligible; and the refusal of some to receive a

donation (110). As a result, a third trial has begin in Sierra Leone, where as of February 2015, up to 60-80 people were being infected, using the plasma donated for the Liberia trial (110).

ZMapp – ZMapp is antiviral monoclonal antibody cocktail that binds to GP and neutralizes the virus and prevents it from entering cells (69). There are three different epitopes on GP1 that the drug targets: one on the glycan cap and two at the base of GP1 (see Figure Seven) (67). Mouse models and studies using non-human primates that were given ZMapp showed a decreased death rate in the treated animals (71; 75; 78). ZMapp was administered to seven patients in the current Ebola outbreak as part of their treatment protocol (75). Five survived and two died, but the drug was given in the context of a comprehensive treatment plan so it is impossible to isolate the effectiveness of the drug (68).

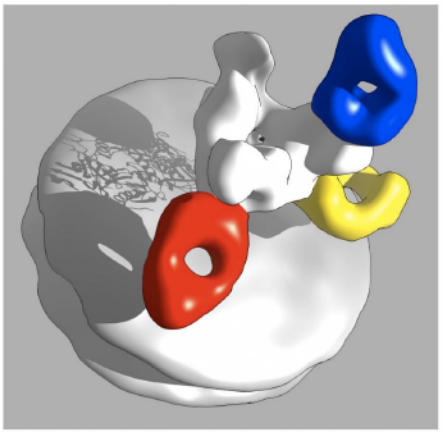


Figure Seven: an image of the epitopes on GP that ZMapp targets. The red and blue antibodies bind near the base of virus, preventing the virus from entering cells. A blue antibody binds to the glycan cap, signaling the immune system to the site of infection.

Source: http://www.pnas.org/content/111/48/16975/F3.expansion.html

One of the major drawbacks with ZMapp is that the drug is manufactured using tobacco plants and the process is laborious and time-consuming (62). ZMapp Biopharmaceuticals, the developer of the drug, is working with the US Biomedical Advanced Research and Development Authority (BARDA) as well as Genetech and Regeneron, two biotech companies, to develop ideas that will increase production. One potential idea is to switch from the current model that uses tobacco plants in Kentucky to manufacturing the drug in China using hamster ovaries. Mapp Biopharmaceuticals also recently signed a $24.9 million contract with BARDA to acquire US Food and Drug Administration approval for the drug and the drug went to clinical trial in February 2015. It is being run by the NIAID at the ELWA2 Ebola Treatment Center in Monrovia, and at the NIH Clinical Research Center in Bethesda. Eligible participants are adults and children who have been diagnosed with Ebola. All patients will be randomized to the treatment group, all of whom will receive three infusions of ZMAPP on sequential days as well as optimized care for an Ebola infection, which includes intravenous fluids, balancing electrolytes, and maintaining blood oxygen and pressure. The control group will receive optimized care only (111). Starting the trial been hampered by the lack of product; all available doses of ZMAPP were exhausted in 2014 (70; 71).

Brincidofovir **–** produced by Chimerix in Durham, North Carolina, Brincidofovir was originally manufactured to treat DNA viruses such as adenoviruses, poxviruses, and herpesviruses (72; 62; 75). In the process of testing the drug for its initial purpose, Brincidofovir was discovered to limit Ebolavirus replication in cell culture (73). The orally administered drug was being used in a clinical trial in the MSF-run ELWA-3 Treatment Center in Monrovia, Liberia. The trial was being run by scientists from the

University of Oxford and uses the following metric to determine success: if under 50% of the patients treated survive the infection, then the drug will be deemed no better than current supportive care. If more than 80% of patients survive, the drug will be considered effective. Fifty percent – 80% survival will warrant further testing. Due to ethical concerns, there is no control group in this study (66; 72). However, as February 2015, the study was halted because there were not enough patients to conduct a statistically significant trial. Furthermore, Chimerix declared that the drug has been deprioritized and they would not be participating in any development of the drug in the future (112; 119).

Faviporavir – A product of Fujifilm in Japan, Favriporavir is an RNA polymerase inhibitor, meaning that the drug thwarts the virus's ability to assemble. The drug was initially developed to treat novel or drug resistant influenza strains in Japan (62; 78). With respect to treating Ebola patients, Favriporavir has shown efficacy in mouse models if it is administered up to six days post exposure, but wasn't as effective in non-human primate models (62; 78; 114). Mouse models for Ebola are not ideal because rodents only develop a mild form of the disease. To overcome this, scientists used genetically engineered mice that were more susceptible to lethal doses of the virus, which muddied the ability to apply the results to the human target population (62). At the time of this writing, the French biomedical company INSERM finished running human clinical trials at the MSF Ebola Treatment Center in Gueckedou, Guinea in which 69 adults and adolescents took the drug for up to 10 days and their outcomes were compared to patients who were treated at the same Center three months prior to the trial start (72; 113). Forty-eight percent of the patients died, but it was unclear if the outcome was related to the amount of viral load measured when they presented or if it was due to the drug. The

results of the trial were inconclusive with INSERM citing that patient viral load may have been more of a determining factor than the drug efficacy. Patients who had lower viral load had better outcomes than those with a higher viral load at the start of treatment, leaving investigators to speculate that the drug could improve outcomes if administered early in infection (113; 115; 119). More data is required to make any definitive conclusions.

AVI-6002 – AVI-6002 is an antiviral therapeutic manufactured by Sarpeta Therapeutics in Cambridge, Massachusetts (74). It works by targeting VP35 and VP24 viral proteins and showed partial protection and prevention of disease in studies using non-human primates. Two Phase I Clinical Trials were just completed and the published results indicate that the drug was safe and well tolerated in 30 healthy male and female Ebola naïve subjects (77).

TKM- Ebola – TKM-Ebola is a cocktail of three small interfering RNA molecules that block the expression of L-protein, VP 35 and VP24 of the Ebola genome (114). The drug is delivered into cell cytoplasm via a lipid-based capsule and prevents the virus from replicating. Tekmira Pharmaceuticals in British Columba developed the drug after they received a $140 million Department of Defense grant in 2010 (75). Studies in lab animals showed that the drug protected against Ebola infection. In January 2014, TKM-Ebola entered into a Phase I clinical trial, but it was put on hold in July, which was lifted in August, after there were signs that some patients showed developed elevated cytokine levels that mimicked those found in Ebola infections (76; 78; 62). A second single arm

trial began in March 2015 led by the University of Oxford in partnership with Sierra Leone Ministry of Health to evaluate its efficacy (116).

rVSV-ZEBOV Vaccine – This vaccine uses a vesicular stomatitis virus (VSV) that has been engineered to expresses Ebola GP instead of its natural surface protein. VSV is a member of the Rhabdoviridae family, which is a distant relative of filoviruses (see Figure Three). It causes disease in cattle, horses, deer and pigs, but is generally thought to be non-pathogenic in humans; at the very least, it causes asymptomatic disease or mild flu-like symptoms. This, along with the fact that there is a low percentage of VSV seropositivity in the general population, makes VSV an attractive viral vector (79).

rVSV-ZEBOV was developed in partnership with the Public Health Agency of Canada and New Link Genetics of Ames, Iowa. New Link went into partnership with Merck in November 2014, with the latter paying $30 million up front for exclusive rights for the vaccine and any of its offshoots. New Link will get $20 million more when the vaccine enters the testing phase (80).

Although rVSV-ZEBOV uses a live virus vector, it isn't a pre-emptive vaccine. In monkey models, the drug was administered 30 minutes after viral exposure; half of animals died. In October 2014, the vaccine went into Phase I Clinical Trials at the Walter Reed Army Institute of Research (82; 83). In November 2014, additional Phase I trials began in Germany, Switzerland, Gabon, Kenya, and Canada (119). The Swiss arm of the trial was put on hold after some subjects complained of joint pain (84). It was expected that trials would resume in January 2015 (81). A Phase III trial was launched in March 2015 that is being run by the WHO, the Guinean Ministry of Health and MSF in which

investigators will utilize a ring vaccination strategy whereby an 'index case' will be identified and all of that persons contacts will be vaccinated. The vaccine will be evaluated by how well it protects the contacts and protects those who they come into contact with (118; 119).

chAd30-EPOV – chAd30-EPOV is a vaccine candidate that was developed by the Vaccine Center for Research at the National Institute of Allergy and Infectious Disease (USNIAID) in Bethesda, Maryland and manufactured by Glaxo-Smith-Kline (86). The original technology for the vaccine was actually developed in part by Okaidos, an Italian company that has been working on Ebola vaccines with the National Institutes of Health since 2011. Glaxo-Smith-Kline bought Okaidos in 2013 for $235 million (85; 81).

The cdAd30-EBOV vaccine uses a modified chimp adenovirus (that is not pathogenic in humans and has been modified not to replicate) as a viral vector that has a single attachment of GP from two Ebola strains on the surface (86). Animal model studies showed that the vaccine was protective. Phase I Trials took place in Maryland and the United Kingdom in September (119). Results from the Maryland trials indicated that there were no safety concerns and the vaccine-induced immune response was in keeping with what was reported from preclinical trials involving non-human primates (86; 87).

Participants in this Phase I trial dose escalation received a single intramuscular shot in one of two different doses. Those who received the higher dose of the vaccine showed higher anti-GP antibody titers to both the Zaire and the Sudan Ebolavirus strains. They also mounted CD4+ and CD8+ TCell responses, which were measured by the expression of cytokines, specifically INF gamma, IL2 and Tumor Necrosis Factor.

Furthermore, those in the higher dose group had a higher proportion of CD8+ TCells, which have been known to confer protection in non-human primates (87).

Phase I Trials chAd30-EPOV also started in October in Mali and Switzerland; with the Mail branch of the trial being run by the Center for Vaccine Development at the University of Maryland Medical School. Phase II trials are set to begin in regions of Africa that are outside the current outbreak zone. Proposed sites include Cameroon, Ghana, Mali, Nigeria and Senegal (119; 86; 87).

There are also plans to fast track Phase III trials that will test the New Link/Merck vaccine concurrently with the Glaxo Smith Kline product. The trials began in March 2015 in Sierra Leone, where 8000 health care workers are to be given both vaccine candidates in a step-wise fashion (88; 119). Another trial in Liberia run by the NIH and the Ministry of Health in Liberia is intended to be a comparative analysis study that was slated to start in March 2015 (119). There will be three groups of patients, each of whom will receive the VSV vaccine, the adenovirus vaccine, or a placebo. No information is available at the time of this writing as to what kind of enhanced treatment the control group will receive (88).

Ad26-EBOV/ MVA-EBOV - Johnson and Johnson entered into partnership with USNIAID and Bavarian Nordic, a Danish pharmaceutical company, to develop this prime-boost vaccine protocol. Johnson & Johnson developed the prime (ad26-EBOV) and Bavarian Nordic developed the booster shot (MVA-EBOV). The vaccine is currently in a randomized controlled Phase I Clinical Trials at the University of Oxford. Johnson & Johnson spent $200 million to fast track production of one million doses that are expected to be available in May 2015. It was recently announced that a second Phase I Trial of the

prime/boost vaccine will be run by Optimal Research in Maryland and they were currently recruiting volunteers as of February 2015 (89; 90).

Other Vaccines – Two other vaccine candidates are in production. Profectus Biosciences in Baltimore Maryland recently completed an Investigational New Drug application for VesiculoVax, their rVSV vaccine. Animal studies showed that their vaccine was 100% protective in non-human primates. The company has been working with the BARDA and the United States Health and Human Services (HHS) since 2007 on Ebola vaccines. Profectus recently received $5.8 million from BARDA and HHS to take their vaccine candidate to Phase I Trials in mid-2015. Including this most recent funding, Profectus has secured a total of $27.9 million to develop their Ebola vaccine. They also received an additional $9.5 million contract from the Department of Defense to develop a trivalent Ebola vaccine (91).

Geovax, an Atlanta company, has also been working on a modified vaccinia virus vector vaccine that is based on the attenuated small pox vaccine that was given to 100,000 people in the 1970's. They currently have grant proposals in to the National Institutes of Health and the Department of Defense (85).

History of Ebola Virus Outbreaks (see Figure Eight)

Two Inaugural Outbreaks

Ebola Hemorrhagic Fever, now known as Ebola Virus Disease, was first discovered during two simultaneous epidemics of the then-unknown causative agent in Central Africa in 1976 (16).

Sudan, 1976(16; 93) The first outbreak was in Nzara and Maridi, Sudan from June–November 1976. The outbreak began when three men who worked in a cotton factory in Nzara became ill and died. Although all three men worked together, they did not live close to one another and had no known contact outside of the factory. Two of the three original cases, known as YB and BZ, are believed to only have transmitted the virus to members of their family who cared for them while they were sick. YG developed symptoms on June 27, 1976 was admitted into the Nzara Hospital on June 30 and died on July 6. BZ was admitted into the hospital on July 12 and died on July 14.

The third case, known as PG developed symptoms on July 18, 1976, was admitted into the hospital on July 24 and died on July 27. PG was active and sociable in his community and is thought to have been the original source of 48 cases and 27 deaths. PG's contacts spread the disease throughout the community of Nzara as well as into the city of Maridi in late July (128 km away) where at least three people were admitted to Maridi Hospital with the Ebola-like symptoms. The virus then spread throughout the hospital to staff who worked there, to other patients and into the community at large. In the beginning of September, there was an additional cluster of six cases and 25 contacts in Nzara. Although these six new cases worked at the cotton factory, they were unrelated

to the three original cases (or any of their contacts) and they reported having no previous contact with anyone who had symptoms consistent with Ebola. Patients in both cities presented with symptoms typical of Ebola: they initially had fever and headache that quickly progressed to diarrhea, vomiting, chest pain and rash (in about half of the cases).

While the cases in Nzara and Maridi had similar clinical manifestations, the transmission patterns in the two cities were very different. In Nzara, Ebola was spread mainly through the contacts of the original three factory workers, while nosocomial transmission was the driver behind the spread of the disease in Maridi. Of the 213 cases in Maridi, 93 of them acquired the disease in the hospital and of those, 72 were staff members who contracted the disease while they were working. By the time outbreak in Sudan was over, there were 67 cases and 31 deaths in Nzara; and 213 cases and 116 deaths in Maridi for an overall Case Fatality Rate of 51%. The spillover event or zoonotic reservoir was never definitively identified for this outbreak, however the cotton factory was implicated as the possible source of the infection.

Zaire, 1976 (52) The second outbreak occurred at almost the exact same time (September to November 1976) in neighboring Yambuku, Zaire (now known as the Democratic Republic of Congo). This outbreak began when the index case, a 44-year-old male schoolteacher, presented at the Yambuku Mission Hospital on August 26 with symptoms that were thought to be malaria. He was given a shot of anti-malarial medication after which his fever abated. On September 1, he developed fever again along with symptoms that were consistent with Ebola. He was admitted to the hospital on September 5 and died on September 8. There were nine additional cases in early September, all of which

appeared to be unrelated with the exception that all had received treatment at the Hospital. It was later determined that 85 cases (out of 288 cases where transmission could be identified) could trace back acquisition of the disease to receiving injections at Yambuku Mission Hosptial; 149 of the 288 contracted the disease through close contact with an infected person; 43 of 288 had both contact with an ill person and a history of receiving injections at the hospital. The disease hit hospital staff particularly hard: 11 out of 17 staff members died and the hospital closed after the medical director and three Belgian missionaries also died.

By the end of the outbreak there were a total of 318 documented cases and 280 deaths with a Case Fatality Rate of 88%. However, the Case Fatality Rate among those cases who became exposed to Ebola via injection was 100%: no one who had exclusive contact with the disease from a contaminated needle survived.

The primary zoonotic event was never identified, and it is unclear if the index case was infected prior to seeking care and brought Ebola into the hospital or if the virus was already in the hospital and he himself was infected there. Be that as it may, the means by which the virus appeared in Zaire has not been identified. It was speculated at the time of the outbreak that the virus was brought directly from Sudan. It is also worth mentioning that the index case had been on a tour in rural areas surrounding Yambuku with mission workers prior to becoming sick. It was reported that he purchased and handled monkey and antelope meat on August 22, and that his family later ate the antelope, but not the monkey. The timing of this bushmeat contact with respect to the onset of his symptoms may fit with the now-known pathogenesis and incubation period of Ebola, however no animal has been implicated as the source of the zoonotic event.

Causative Agent and Control in the Two Inaugural Outbreaks (52; 93) Ebola was identified as the causative agent in the first two outbreaks when the virus was isolated from patients from Sudan and Zaire. Analysis showed that two distinct subtypes, the Sudan Ebolavirus strain and Zaire Ebolavirus strain, caused the Sudan and Zaire outbreaks respectively. After the identification of this new pathogen, a team from the Center For Disease Control joined a group of international scientists to investigate and control the outbreak in Zaire. The team was known as International Commission for the Investigation and Control of Ebola Hemorrhagic Fever in Zaire. It was this group that gave the virus the name Ebola, a namesake of the Ebola River, which runs in Northwestern DRC, close to where the outbreak occurred (52; 94; 95).

Containment of the Outbreaks (94) There were several factors that contributed to the successful termination of the first outbreak in Zaire. All Commission activities and logistics were coordinated with the sole intention of ending the outbreak. They maintained open channels of communication with the Minister of Health of Zaire: they met with him daily to share information, to update him on progress, and to delineate upcoming action plans. Team members also worked closely with local leaders, explaining what they knew and promised to remain in the area until the outbreak was over. Teams went into the field immediately to find and isolate active cases and trace contacts. They also made recommendations and advised on abbreviated funeral rites that limited transmission of the virus while preserving the cultural context of traditional burial practices.

However, it was reported by the team that the most effective mechanism to control and end the outbreak was house-to-house visits. While the ostensible purpose of these visits was to trace contacts and find new cases, they were also imperative to establish trust with local communities. Many infected patients and their contacts fled out of fear of the disease and out of suspicion of Western medicine, opting instead to seek treatment from traditional healers. An outbreak cannot be ended if patients are transmitting the disease out of the reach of infection control and in an attempt to assuage uneasiness and distrust, clinicians from the local university hospital were included as an integral part of the international teams. By the time the Commission was disbanded at the end of the outbreak, they had visited 550 villages at least twice over a 2-month period and a third visit was made in the villages where Ebola was found.

Evidence of Endemic Ebola in the Two Inaugural Outbreaks (51) Although the outbreaks in 1976 were the first Ebola outbreaks on record, it is possible that there had been earlier Ebola occurrences in remote regions of Africa and outside epidemiologic surveillance. A retrospective investigation from a single, isolated Zaire Ebola case in 1977 led researchers to believe that there was a possibility that Ebola Virus Disease was endemic, but sporadic, in the Northern part of the Democratic Republic of Congo since 1972.

The investigation began when a single Ebola case presented in Mission Hospital in Tandala, Zaire in June 1977. The patient was a nine-year-old girl who lived with her family in Bonduni Village, 20 km from Tandala, on the border of Zaire and the Central Africa Republic. She was admitted to the hospital after she developed fever, abdominal pain and hematemesis. She was clinically diagnosed with Zaire Ebolavirus, immediately

isolated, and standard barrier care methods were implemented. Her family did not report that they had traveled outside of the village before she became ill; no one else in her family or in her village suffered from a similar illness for up to four weeks before the onset of the little girl's symptoms; and there were no secondary cases identified among her contacts. Her family members were tested after the little girl's death and blood and serum analysis revealed that none of them had anti-Ebola antibodies.

A retrospective investigation of hospital records revealed that there was one other patient, a 12-year-old girl from Bowabili, 30 km south of Tandala, who had been treated for febrile hemorrhagic disease five months later in November 1977. This child's little sister had also been ill at the same and serological testing on the little sister revealed that she had Ebola antibodies, although no other family members did. Furthermore, it was also found that a physician from Tandala Hospital, where both girls were treated, also had Ebolavirus antibodies. It is suspected that he contracted the disease when he lacerated a finger while performing an autopsy in 1972 on a patient who died of hemorrhagic illness. The doctor became sick 12 days after the autopsy with symptoms consistent with Ebola, but he recovered approximately 10 days after fever onset. Furthermore, analysis of villagers in a 40 km radius of Tandala showed that 7% of those tested (79 people) had antibodies to Ebolavirus although none of them gave a history of clinical Ebola Virus Disease.

The nine-year-old girl, the twelve-year-old girl and the doctor had no connections either to each other or to the original outbreak in Zaire in 1976; their infections were neither a result of nosocomial transmission nor household transmission. Consequently,

researchers surmised that Ebola may have been circulating in the region as early as 1972 and could be endemic.

1995 – 1996 Zaire Ebolavirus Outbreaks

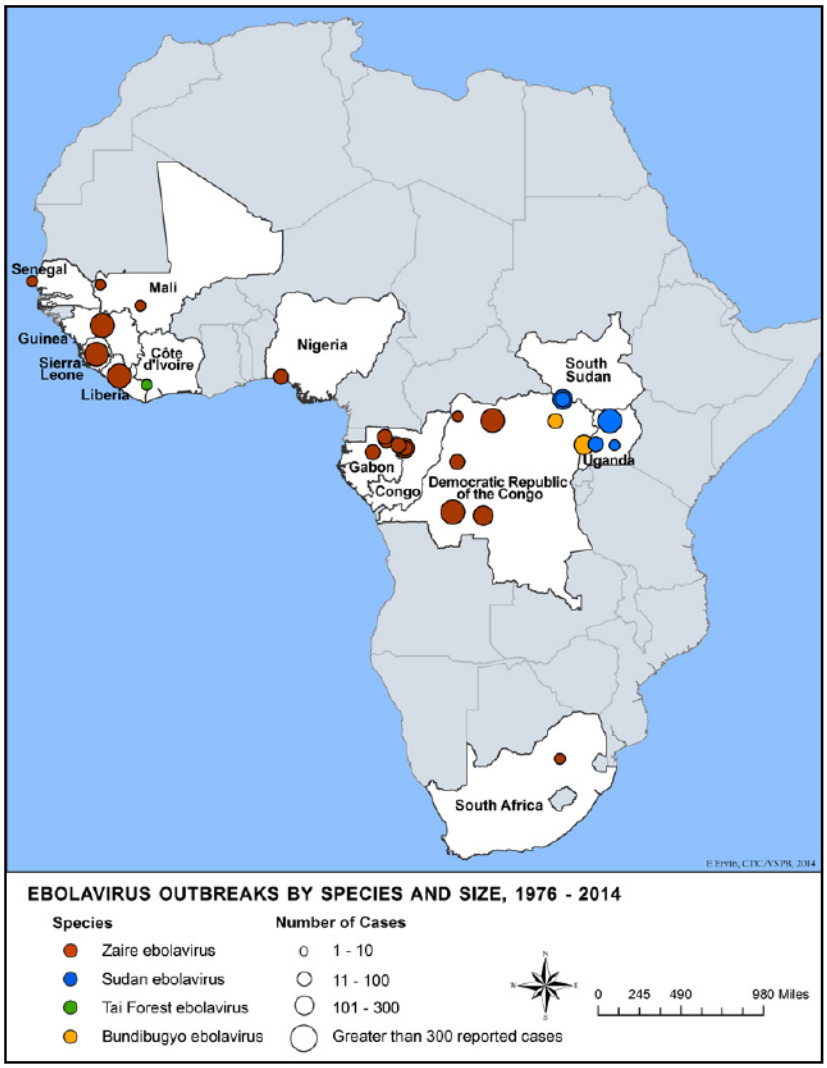
Kikwit, 1995 (96; 101) After 1977, the virus went 'silent' for 15 years, with no outbreaks recorded until the Zaire strain emerged in Kikwit, Democratic Republic of Congo from January – July 1995. The index patient was thought to be a 42-year-old man who came into contact with the virus' unknown natural reservoir while working in a charcoal pit. He became ill on January 6, 1995 and was admitted into Kikwit General Hospital on January 13. He transmitted the virus directly to three immediate family members; ten of his extended family members were identified as secondary cases over the next nine weeks. These initial cases and their contacts spread the virus throughout the community via person-to-person and funeral transmission.

The chain of infection eventually led to Kikwit Maternity Hospital in mid-March when there was a small nosocomial outbreak, initially diagnosed as dysentery, among nine employees. Towards the end of April, there were cases of Ebola reported among the surgical staff at Kikwit General Hospital, all of which were traced back to a surgery that was performed on a lab technician who was employed at the Maternity Hospital.

The virus was also introduced into Kikwit General by two other sources. The first was through a nurse from the Maternity Hospital who was admitted into Kikwit General as a patient after she was nosocomially exposed by an obstetric patient; the second introduction into Kikwit General was through an obstetric nurse who was exposed while caring for a cesarean patient. By the end of the outbreak, there were 315 cases and 256 deaths, 25% of whom were health care providers.

It is thought that the lag time between the presentation of the first cases and investigation of the disease fueled the growth of this outbreak. A local ad-hoc committee responsible for investigating the outbreak wasn't formed until May 1, 1995, five months after the index case, and it was tasked to investigate an epidemic of dysentery deaths, not Ebola. It was only after the committee consulted with a member of the Ministry of Health of the Democratic Republic of Congo, J.J. Muyembe-Tamfum, who had worked on the 1976 outbreak, that Ebola was even considered as a possible causative agent. Samples from 14 patients were sent to the Center For Disease Control in early May; Ebola was confirmed as the cause of the outbreak on May 9, 1995. At that point, international teams were brought in to manage, control and end the outbreak.

Identifying cases and tracing contacts proved to be challenging considering that no public health surveillance infrastructure in Kikwit existed. There were other obstacles as well: there were no telephones and very few transportation options. There was a propensity for patients to hide, deny or otherwise conceal their illness for fear of stigma. Health education was hampered by the lack of mass media, so information campaigns were rolled out using flyers, posters, banners and broadcast messages via megaphone in the streets. As rudimentary as the methods implemented may have been, they worked. On July 16, the last Ebola patient died, only a few months after the CDC and international health community were called in. Their quick success reaffirmed that education, surveillance and the use of proper barrier-nursing practices can interrupt Ebola transmission rapidly and effectively.



Source: http://www.cdc.gov/vhf/ebola/outbreaks/history/distribution-map.html

Figure Eight: Location of Ebola Outbreaks since 1976

Zaire 1990's (98; 99) There were three other Zaire Ebola outbreaks in the mid 1990's, all of which occurred in northeastern Gabon (see Figure Nine). The first occurred in two separate waves in December 1994 and January 1995 in and around Mekouka, Gabon, a town located close to the border of Cameroon. The first wave of Ebola cases originated in three gold mining camps located at the edge of a rainforest when 32 miners became ill. They traveled 100 km by river to the hospital in Makoku to seek treatment where they were initially diagnosed with Yellow Fever and immediately vaccinated. Retrospective testing of samples from those patients revealed that Zaire Ebolavirus was the causative agent. Against medical advice, one of the miners checked himself out of the hospital to seek care from a local traditional healer (a nganga) in the nearby village of Mayela. The escaped patient and the nganga were responsible for the second wave of 16 cases. Each one of the 16 could trace the transmission event back to caring for a relative in the hospital, sleeping at the nganga's home or close contact with individuals who were employed at the hospital. By the time the outbreak burned itself out, there were 51 cases and 31 deaths.

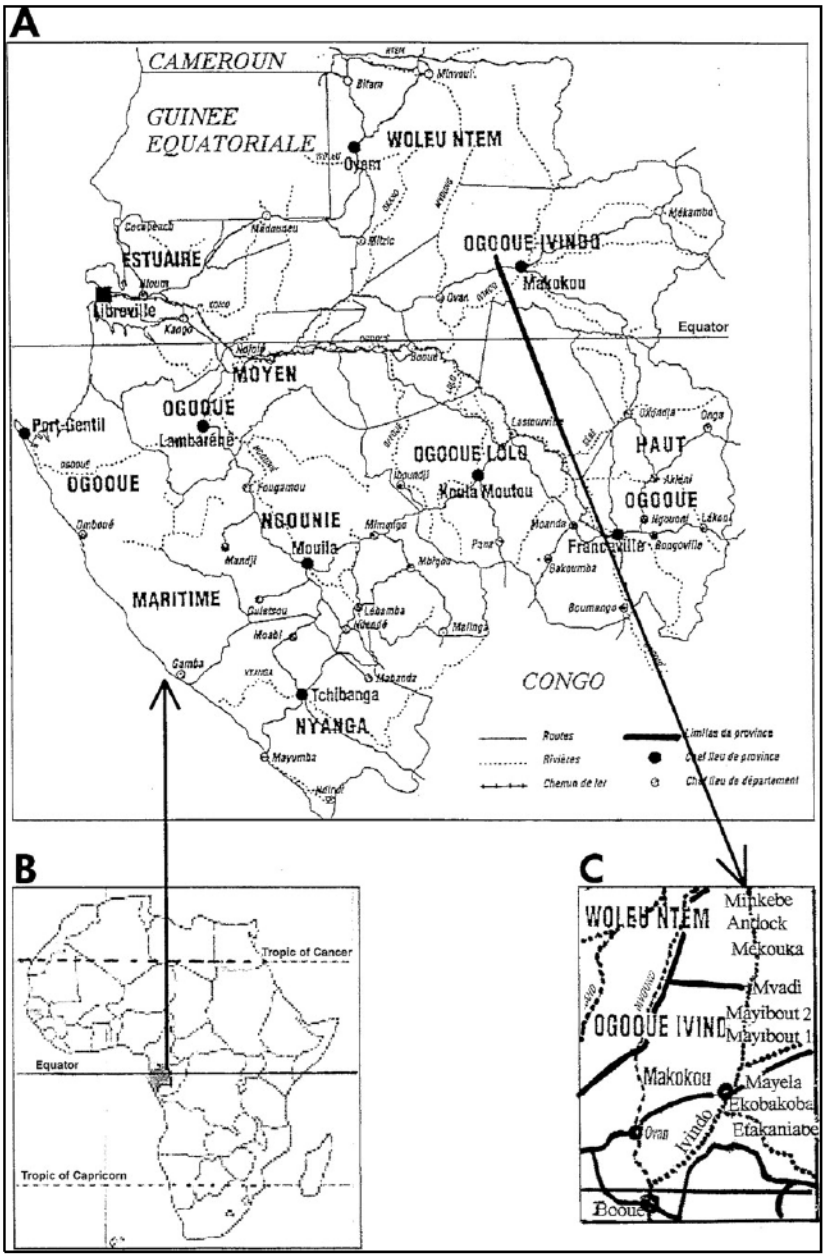
While the zoonotic reservoir for this outbreak was not identified, there were reports of a large number of deaths in a local population of gorillas and an anecdotal tale from one of the patients regarding a bizarrely behaved chimpanzee that was later killed. Neither story could be verified with gorilla cadavers or skeletons in the forest in question. No animals collected in the area surrounding the gold mines revealed Ebola infection, but mines are a known habitat for bats.

The second Zaire Ebolavirus epidemic in Gabon occurred in early February 1996 in the village of Mayibout 2, Gabon, which lies in between Mékouka and Andock (the

location of the gold mines where the first epidemic broke out) and Makokou (where the patients from the gold mines were treated). The outbreak is thought to have begun when 18 people carried and helped butcher a chimpanzee carcass that they found in the forest. It was said that the meat was rotted and the chimpanzee appeared to be ill before it died. After handling the meat, the patients and their contacts became ill with fever, headache, bloody diarrhea and were sent to Makokou Hospital, despite governmental instructions to the contrary. The bodies of the 4 patients were returned by river to Mayibout2; a fifth patient, who escaped from the hospital while symptomatic, died when he returned home to Mayibout2. The bodies of the initial patients were buried according to traditional burial ceremonies and without any special precautions to avoid viral transmission. The disease eventually spread to the neighboring villages of MayiboutI and Mvadi before it ended. By the end of the outbreak, 31 cases were identified and 21 of them died.

The third outbreak occurred in Booue, Gabon 120 km southwest of Mekouka, as early as July 13, 1996 when a 39 year-old hunter in a logging camp became ill with Ebola like symptoms. Six weeks later in the end of August, a second hunter died with similar symptoms and 12 days after that a third hunter was taken to the hospital. The third patient left the hospital to seek treatment from an nganga in the nearby village of Balimba, where he died. The nganga and his nephew and some of his other patients also became infected and spread the disease to towns and villages in the surrounding area. The zoonotic link was never formally identified, but several chimpanzee carcasses were found in the forest areas at the time of the human outbreaks, and tissue samples from one of them tested positive for Ebola antigens.

This outbreak was not only contained to the Gabon. A physician who performed an endoscopy on an Ebola patient from Booue became ill. Apparently unaware that he had contracted Ebola, he flew to Johannesburg, South Africa for treatment, where he infected a nurse who cared for him. There were no other know cases associated with the Johannesburg nurse or the doctor. The epidemic was declared over in Gabon in March 1997, with a total of 60 cases and 45 deaths.



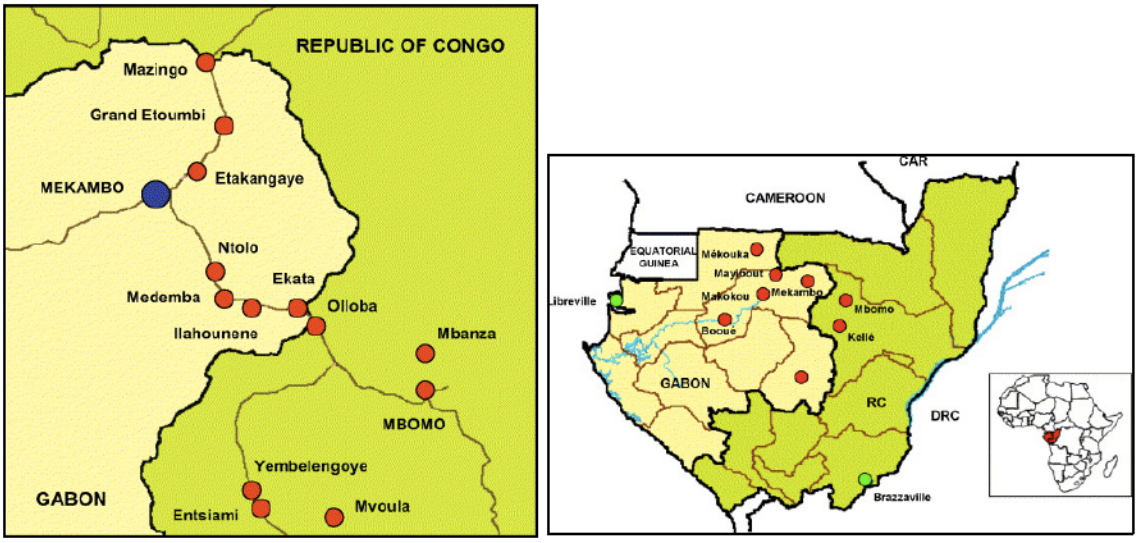
Source: http://jid.oxfordjournals.org/content/179/Supplement_1/S65.full.pdf+html

Figure Nine: Geographical locations of the 1995-1996 Zaire Ebolavirus outbreaks in Gabon (99).

Zaire Gabon/Democratic Republic of Congo 2000-2004 (98; 100) The period of 2000 – 2004 saw several outbreaks of Zaire Ebolavirus (see Figure Ten). The first outbreak was in the area surrounding the city of Mekambo, Gabon, which is located where Gabon and the Republic of Congo share a border. Rather than one large epidemic of human to human transmission events that can be traced back to one zoonotic spillover event, the cases of Ebola that occurred from October 2001 – May 2002 in Mekambo area were a series of independent outbreaks stemming from six different spillover events, each of which were related to hunting.

The first spillover occurred in the village of Mendemba in Gabon on October 21, 2001 when a hunter handled an antelope carcass that he found. At the time of his presentation to the hospital with febrile symptoms, the index case did not draw the attention of health authorities as a possible Ebola patient and was not diagnosed as such. It is unclear what his diagnosis was, but he was retrospectively diagnosed with Ebola. This initial case generated several secondary infections, but the disease did not draw the notice of regional health authorities until six members of the same family fell ill and died over a three-week period. On November 30, samples from this family were sent to France for analysis; Zaire Ebolavirus was identified as the causative agent on December 8, at which point the WHO was notified. In the following days and weeks there were several more suspected Ebola patients being admitted to Mekambo Hospital as well as to Mekouka Hospital, most likely the result of community based and nosocomial transmission. Additionally, there were reports of 20 dead gorillas and four chimpanzees in the rainforest of the same district.

The second transmission event occurred on November 28, 2001 in the village of Ekata in Gabon when hunters manipulated an antelope; the third transmission event occurred on December 1 in Olloba, Democratic Republic of Congo when hunters butchered a gorilla carcass. Three weeks later the fourth transmission event happened in Ekata on December 22 from an unknown source; the fifth on December 29 in Etakangaye, Gabon when hunters handling a chimpanzee carcass became exposed. The sixth identified zoonotic transmission event occurred on March 27, 2002 when hunters from Grand-Etoumbi butchered and ate a gorilla carcass they found in the forest. By the end of these sequential outbreaks that took place from October 2001 – March 2002 there were 65 cases and 53 dead in Gabon and 57 cases and 43 dead in the Democratic Republic of Congo. All but two cases were epidemiologically linked to an official chain of transmission. Two gorillas that were butchered by one of the index cases in this series of spillover events were found positive for Ebola, but these were the only animals positively identified as being infected.



Source: http://www.sciencedirect.com/science/article/pii/S1286457905001437

Figure Ten Map of the border region of Gabon and the Democratic Republic of Congo; the site of six independent Ebola spillover events from October 2001 – May 2002. (98)

The second of the Zaire Ebolavirus outbreaks that occurred from 2000 – 2004 affected the area surrounding Mbomo. There were two zoonotic events, one in Yembelengoye and another in a gold-mining camp in Mvoula following the handling of animal carcasses. From December 2002 to May 2003, there were 143 cases and 128 deaths associated with this outbreak. The third outbreak to occur during this period was in Mbanza, Democratic Republic of Congo when cases from an unknown source were reported between October and December 2003. There were 35 cases and 29 deaths.

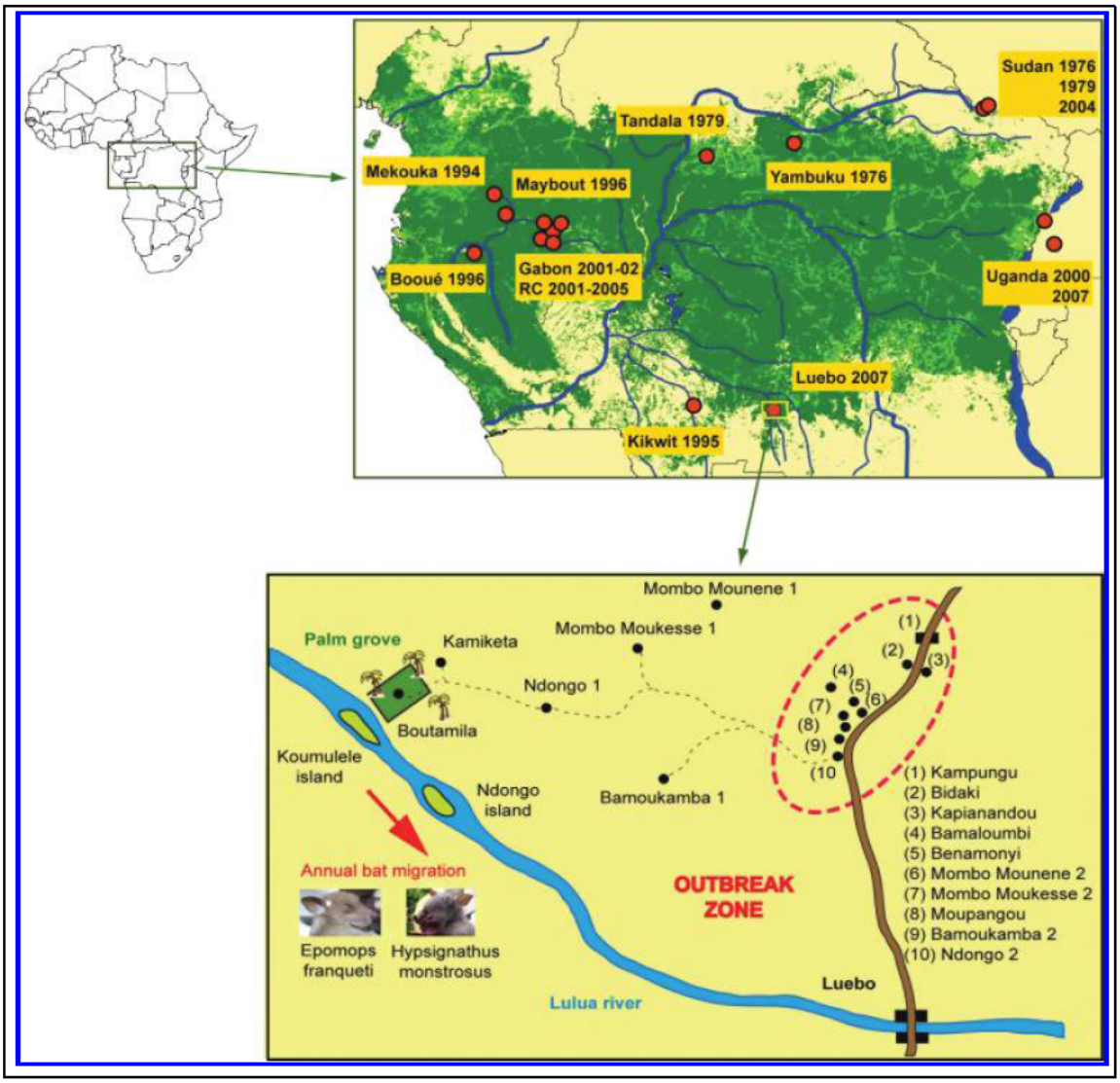
Zaire in Democratic Republic of Congo 2007 (54) The last large Zaire Ebolavirus outbreak to occur before the 2014 Ebola epidemic occurred from May - November 2007 in the Democratic Republic of Congo. The epicienter of the outbreak was located in a collection of 10 villages that are settled on the road between Luebo and Mweka (see Figure Eleven). Unlike in past outbreaks in Central Africa, there were no reports of simultaneous mortality among non-human primates or other fauna in the forests adjacent to the outbreak epicenter.

There was bat activity around the time that this outbreak began. Each year thousands of fruit bats migrate southeast up the Lulua River towards Angola and Zambia and roost for a month on the islands of Ndongo and Koumuelele. There is also a palm oil plantation close to the river and though it is dormant, it is still a place where bats can feed undisturbed. It is during this roosting period that hunters are known to kill the bats and sell them for food. The behavior of index patient was retrospectively traced to his purchase and consumption of freshly killed bats.

The index case in this outbreak was a man from Bamoukama2 village who regularly bought bats for consumption at the Mombo Mounee2 market and reporting having regular contact with bat blood. He developed very mild symptoms (a headache and a fever) and did not die (it also appears that his wife did not become ill either), but he did transmit the virus to his four year-old daughter who fell ill with vomiting, diarrhea and high fever on June 12, 2007 and died four days later. The child was given a traditional funeral, in which the body is washed and touched by mourners. One of the women who assisted in the preparation of the body was a 55 year-old woman who became ill with typical Ebola symptoms and died on July 3, 2007. Eleven of her family

members also became ill and died. From this cluster of cases the virus spread throughout the community.

Given the remote location of the outbreak (villages in this community are three-four hours away from the main road and only accessible by motorbike or by foot), and the delayed detection of cases, the international response did not begin until September 2007. Ebola was not determined to be the causative agent until September 10, 2007. It was never confirmed if the index case, his daughter or any of the earliest cases in the outbreak did indeed have Ebola. Ebola was identified as the causative agent on September 10, 2007 from samples that were collected on August 22, 2007. By the end of the outbreak in November 2077 there were 260 cases and 186 deaths.



Source: http://online.liebertpub.com/doi/abs/10.1089/vbz.2008.0167

Figure Eleven. Location of the 2007 Ebola Zaire Ebolavirus outbreak. Each of the 10 villages has a twin village in the forest zone. In essence each village has two parts, one in the forest (village 1), and the other near the road (village 2). Villages2 offer healthcare, education, civil services, shops, and markets. Villages1 agricultural and animal products to villages2, where they are sold in the markets. The main market is held every Monday in Mombo Muonene 2. It is on the trail from villages Bamoukama 1 and 2 where it is speculated that the father carried his daughter on his back and possibly transmitted Ebola. (54)

Sudan Ebolavirus (101; 122) Although not as prevalent as Zaire Ebolavirus, the Sudan Ebolavirus strain has caused six outbreaks since 1976 including the largest Ebola outbreak ever recorded prior to 2014. It began in late August, 2000 in Uganda when the first presumptive case was identified as having Ebola-like symptoms. However, the outbreak wasn't noticed or reported to the Ministry of Health in Kampala until October 8, 2000 when a cluster of cases was identified in St. Mary's Hospital in Lacor, Sudan. The outbreak region was large: the virus found its way from the epicenter in Gulu to Massindi and Mbarara; an area that covered 31000 sqkm and 1.8 million people. The last case was reported on January 9, 2001 and as of January 23 were 428 cases and 173 deaths.

West African Outbreak 2014

Chronology

January - March 2014 The outbreak in West Africa began slowly in the remote regions of Guinea in December 2013, but it didn't take long for it to escape the confines of Guinea and fan out into Sierra Leone, Liberia, Mali and Nigeria (6; 7). Retrospective analysis revealed that the putative index case was a two-year-old boy in Meliandou, a village in the city of Gueckedou, Guinea (208; 212). It is unclear how he became infected, but it is thought that he was exposed to the virus through the handling of bats. The manner in which the virus was transmitted to the index notwithstanding, the chain of human-to-human transmission has not been broken since the primary spillover event in December. As of March 35, 2015 there have been 24,907 suspected and probable cases and 10, 329 confirmed deaths, making this outbreak the largest Ebola epidemic ever recorded (98).

While the outbreak was in its embryonic stages in the early months of 2014, cases began to mount in hospitals in Gueckedou, Macenta and Kissidougou. Physicians initially suspected that cholera was the causative agent and while there were several patients who did test positive for the disease (128; 208). Befuddled doctors soon became suspicious that the illness in question was not cholera (2; 3) but rather some kind of 'mystery disease,' and The Ministry of Health of Guinea was notified about a circulating disease that was characterized by fever, diarrhea, vomiting and high mortality (3). On March 14, 2014, a Ministry of Health team was sent to Gueckendou to investigate and two weeks later, Zaire Ebolavirus was identified as the causative agent. On March 23, 2014, the World Health Organization in Geneva was officially notified of the outbreak (1). At that

point in time there were 86 cases and 59 deaths in the Gueckedou, Macenta, Nzerekore and Kissidougo districts of Guinea (124) (unless otherwise noted, case and death tallies include confirmed, suspected and probable). See Figure Twelve

Geographic distribution of Ebola haemorrhagic fever in Guinea

Source: http://www.afro.who.int/en/clusters-a-programmes/dpc/epidemic-a-pandemic-alert-and-response/outbreak-news/4064-ebola-virus-disease-in-guinea-24-march-2014.html

Figure Twelve. From its beginnings in the small village of Meliandou in southeastern Guinea, Ebola spread to the neighboring regions of Kissidougou and Macenta, but it was only a matter of weeks before the virus made its way in the capital city of Conkary (127) and into the Lofa district in neighboring Liberia (125). This map represents the state of viral spread as of March 24, 2014. While there were suspected cases at this time in Sierra Leone, they were ultimately diagnosed as Lassa Fever. Ebola was not confirmed in Sierra Leone until May 2014 (138).

By the end of March, Ebola left the confines of rural Guinea and crossed borders. On March 27, 2014, Ebola spread to Conkary, the capital of Guinea when four men who had attended their brother's funeral in the central Guinean town of Dabola returned to city and began to exhibit symptoms consistent with Ebola. While all four tested positive for the virus, it was not confirmed if the dead brother had Ebola himself, although he did exhibit symptoms of hemorrhagic fever before he died (210; 211; 125).

On March 29, 2014, Ebola was first recorded in Liberia when seven suspected cases were detected in the Foya district of Lofa County. Two of these cases tested positive for Ebola, one of whom, a 35-year-old woman, became ill after she returned from a trip to Guinea, where she presumably contracted the virus. Before she died on March 31, 2014 she was cared for by her sister, who in turn became sick herself. It is unknown if the sister also traveled to Guinea and contracted the virus there or if she was exposed through direct contact with her sister in Liberia (125; 126).

Around the same time, a second woman brought Ebola into Lofa County after she visited a Guinean market (119). She developed symptoms consistent with Ebola while she was in Guinea, at which point her sister traveled from Liberia to pick her up and brought her home. Eventually, the sick sister was admitted into Foya-Borma Hospital where she died on March 20, 2014. Soon after, the sister became symptomatic, and concerned about her condition, took a taxi to see her husband who was migrant worker at the Firestone rubber plant located outside of Monrovia, the capital of Liberia (population one million people). The sister was symptomatic during the 12-hour taxicab ride (a 360 km journey) from Lofa County to Monrovia and exposed the driver as well as five other people along the way, all of whom later died of the virus. After she arrived in Monrovia,

she caught a ride by motorcycle to Firestone (the fate of the bike driver remains unknown) (132) where she was hospitalized. On March 30, 2014, Firestone alerted the Liberian Ministry of Health that there was an active case of Ebola on the 120,000-acre plantation. On April 1, 2014 the woman's husband and children were put under quarantine, and although one of the children developed Ebola-like symptoms, no one in the family ever tested positive for the virus.

After Ebola was officially identified, the WHO headquarters in Geneva sent thirty-eight epidemiologists, logisticians and data managers (124; 127) to support the search and management of cases across the entirety of the southeastern region of Guinea. The WHO West African Regional Office in Brazzaville, Congo primary task was to deploy personnel to affected regions to support the efforts of Ministries of Health and to guide control efforts on the ground. To that end, together they began making needs assessments and implementing a coordinated response to the outbreak (124; 127). The Ministry of Health of Guinea established an isolation facility in Gueckedou, and Rapid Response Teams in Conkary conducted contact tracing and 'sensitized' health care workers and affected villagers about Ebola and how to reduce transmission (124; 127). After cases were detected in Liberia, a National Task force was established to lead the response that included members of the WHO, the International Red Cross, Samaritan's Purse, Pentecostal Mission Unlimited and UNICEF (125). The team worked together to distribute Personal Protective Equipment to 41 health care facilities; to strengthen infection prevention and control protocols in Foya Hospital; and to train health care workers in Montserrado County on how to treat and isolate Ebola patients. Personal protective equipment and medical supplies were also sent to Bong and Nimba counties

(127). However, rather than appointing Dr. Pierre Formety, the WHO's top Ebola authority as the coordinator of the regional response, the West African office chose an official from the Guinea WHO Office who had never before been involved in an Ebola outbreak (3).

Médecins Sans Frontières, Switzerland (MSF) was already working in the field in Gueckedou on a malaria project when the outbreak began in Gueckedou and immediately stepped in to care and treat Ebola patients (3). MSF has a long history of handling hemorrhagic disease outbreak control efforts in Africa (source: msf.org). They were on the ground in Kikwit in 1995; Gabon in 1997, 2001 and 2002; the Democratic Republic of Congo in 2002, 2005, and 2007; Uganda and the Democratic Republic of Congo in 2012; Uganda for the Bundibugyo outbreak in 2008; and Durba, Democratic Republic of Congo for a Marburg outbreak in 1999. They also had a pivotal role in the control efforts during the outbreak in Gulu, Uganda in 2000-2001.

By the end of March 2014, MSF had 60 international doctors, nurses, logisticians and hygiene and sanitation experts working in MSF-run Ebola Treatment Centers in Gueckedou, Macenta and Conkary, Guinea. They sent 40 tons of equipment to Guinea including medicines, medical equipment and the supplies that were needed to isolate patients, put sanitation measures in place and to protect health care workers. MSF also provided logistical support to the Liberian Ministry of Health in Monrovia. In addition to caring for patients who were showing signs of infection, MSF teams were tracing contacts and educating communities on the disease itself and infection control (129).

MSF was keenly aware that the geographical spread of the disease in West Africa far exceeded that of previous outbreaks and that there was the potential for the epidemic

to spiral out of control. In a press release issued on March 31, 2014 the organization warned that West Africa was "facing an epidemic of a magnitude never before seen in terms of the distribution of cases in the country." In particular, they were concerned about the unusual spread of the disease into urban settings "because it will greatly complicate the tasks of the organizations working to control the epidemic" (129). In response to MSF's warning, on April 1, Gregory Hartl of WHO responded that the outbreak was "relatively small still" and cautioned the use of alarmist rhetoric saying "we must be careful with how words are used… for now what we see are sporadic cases, we cannot call it an epidemic" (128).

April 2014 (130; 131; 132; 133; 134; 135; 136) Transmission throughout the month of April was localized, but intense. In Guinea, the transmission appeared to be actively contained in Conkary, Gueckedou, Macenta, Kissidougou, Dabola, and Djingaraye; while in Liberia, the majority of reported cases were in Lofa and Margibi counties (38% and 27% respectively), with Bong, Nimba, Montserrado and Grand Cape Mount reporting fewer, but consistent, cases.

Forty-four more experts were deployed to Guinea, Liberia and Sierra Leone (130), for a total of 50 across the region (134) but it appeared that the majority of the control efforts embarked upon by the regional WHO offices and the national governments of Liberia, Sierra Leone and Guinea revolved around holding meetings, making assessments, and developing preparedness plans (134). On April 2, the Chief Medical Officer of Liberia visited Lofa County and held meetings with local government officials (132; 134). The National Task Force in Liberia conducted daily coordination

meetings with response partners (133). The WHO Country Office in Liberia conducted a needs assessment with the Ministry of Health in order to get a handle on equipment and materials gaps (133). The Ministry of Foreign Affairs of Guinea met with the Minister of Health, local WHO representatives, although the content of the meeting was not reported (135). There was a cross border meeting between Liberia and Guinea where epidemiological surveillance and contact tracing along borders were discussed (136).

By the end of April, Guinea reported 58 cases and 24 deaths in Conkary; 127 cases and 91 deaths in Gueckedou; 22 cases and 16 deaths in Macenta; six cases and five deaths in Kissidougou; and four cases and four deaths in Dabola (136). In Liberia most of the 35 cases were in Foya, which was, at that time, considered the epicenter of the outbreak in Liberia. Although there had been several suspected cases in Sierra Leone in March, April and May, most of those turned out to be Lassa Fever (134).

	Guinea		Liberia	
	Cases	Deaths	Cases	Deaths
March (131)	122	80	8	2
April (136)	218	141	35	Not reported

May 2014 Throughout the latter days of April and into the middle part of May, it appeared that the outbreak was under control. Although incident case counts were increasing, growth wasn't explosive. Gueckedou was the only area in Guinea where the active transmission of the disease was still being reported. By May 18, two incubation periods (42 days) had passed since the isolation of the last reported cases in Djinguiraye, Dabola and Kissidougou. In Macenta, there had not been any new cases since April 9, 2014 and Conakry had not seen any new cases since April 26, 2014. There were not any

recorded cases in Sierra Leone and Liberia had only 12 total cases and nine deaths with all suspected contacts and patients in isolation since April 9. The WHO was confident enough to declare that the Ebola outbreak would be over in Liberia by May 22, 2014 (137).

Those sanguine predictions were to be very short-lived. On May 29, one week after the WHO predicted the end of the outbreak, The Ministry of Health in Sierra Leone and the WHO reported sixteen cases in the Koindu chiefdom in the Kailahun District, which lies on the border with Guinea (see Figure 13) (138). The first recorded case was a young woman with hemorrhagic symptoms who traveled from Koindu to Kenema Government Hospital on May 23, 2014. She had a miscarriage and was also suspected of having Lassa Fever. Further investigation revealed that she had recently attended a funeral of a traditional healer who was treating Ebola patients in Guinea. While no nosocomial transmission was officially reported from this one female patient, there were 13 other women who contracted Ebola from that funeral, all of whom brought the virus into Sierra Leone (138). There is thought to have been at least four different clusters of cases identified among these 13 women, and the contacts of these clusters are believed to have spread the virus throughout Sierra Leone to Kenema, Bo, Daru, Kailahun, and the Pehe Bongre, and Jawai Chiefdoms in the eastern district of the country (139).

By the end of May, there were 291 cases and 193 deaths in Guinea; 50 cases and six deaths in Sierra Leone and while there were cases in Liberia, the numbers were not reported due to "changes in reclassification, retrospective investigation, consolidation of cases and laboratory data, and enhanced surveillance" (140). In addition, on May 2, the WHO began reclassifying past case tallies due to consolidation of case, contact and

laboratory data, enhanced surveillance activities, and contact tracing activities. Furthermore, the recent introduction of Ebolavirus serology to test RT-PCR negative clinical cases also changed the final number of laboratory confirmed cases. Therefore, the case and death numbers reported did not increase or decrease in a linear manner over time.

	Guinea		Liberia		Sierra Leone	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
March (131)	122	80	8	2		
April (136)	218	141	35	Unknown		
May (140)	291	193	Not available due to reclassification		50	6

June 2014 On June 1, four days after the first cases in Sierra Leone were recorded, there were a reported 79 cumulative cases and six deaths in the Kailahun, Kenema, Koinadugu, Bo and Moyamba districts in Sierra Leone as well as five cases in the capital of Freetown (140). On June 2, six suspected Ebola patients were taken out of the hospital by their families in Koindu, a town in the Kailahun District (191). Staff and doctors at the clinic had tried to stop the families, but they had been "aggressive" and apparently feared that their loved ones would die a lonely death. The removal of these infectious patients from isolation all but guaranteed that not only would the patients die without proper treatment, but also that the family members who cared for them would be exposed to the virus, as would anyone who also provided care and/or participated in their funerals. Furthermore, it was fairly likely that these cases fell outside of the Ebola surveillance parameters and escaped detection, which also means that all contacts of these six patients went unreported and unfollowed as well, furthering the spread of disease in the community.

Source: http://www.nationsonline.org/oneworld/map/sierra_leone_map.htm

Figure Thirteen: Ebola finally made it into Sierra Leone in late May after a group of 13 women attended the funeral of a natural healer in Guinea who was known to treat patients who had Ebola. The direct and peripheral contacts of these 13 women sparked the spread of the disease to Kenema, Bo, Daru, Kailahun, and the Pehe Bongre and Jawai Chiefdoms in the eastern district (138; 139).

In response to the surge of cases in Sierra Leone, the WHO sent six international experts to Sierra Leone to assist in the areas of coordination, epidemiology, social mobilization, case management/infection prevention and control, data management and logistics. There was just one isolation facility located in Kenema, but there were plans to build two more in Daru and Koindu (143). On June 3 2014, Guinea, Sierra Leone and Liberia agreed to reinforce cross-border surveillance and communication tools to address community resistance (142).

Meanwhile in Guinea, on June 1, 2014 it was reported that the virus had spread outward from Conkary into the previously untouched districts of Telimele (19 new cases and five deaths) and Boffa (two deaths), both of which are on the coast next to the capital (143). New cases continued to be reported in Conkary, Gueckedou and Macenta. In an effort to stem transmission in Guinea, the WHO redeployed five additional experts to the affected areas (142) to actively search for cases and follow-up with contacts and to establish isolation facilities in Télimélé. A team of social mobilization experts was also deployed to support public health awareness with an emphasis on addressing community resistance in some villages (144).

During the first weeks of June there were no new cases recorded in Liberia. Then from June 11 – June 16 nine new cases surfaced and five deaths were recorded in Lofa (144). On June 17, 2014 the first Ebola cases were recorded in Monrovia, Liberia when seven deaths were reported (145). Among them was a nurse who died in Redemption Hospital in the Monrovian slum of New Kru Town, who also infected four other people from her household. The detection of Ebola in Nu Kru Town may have been the tipping point for the explosion of cases in Liberia; living conditions in slums is conducive to the

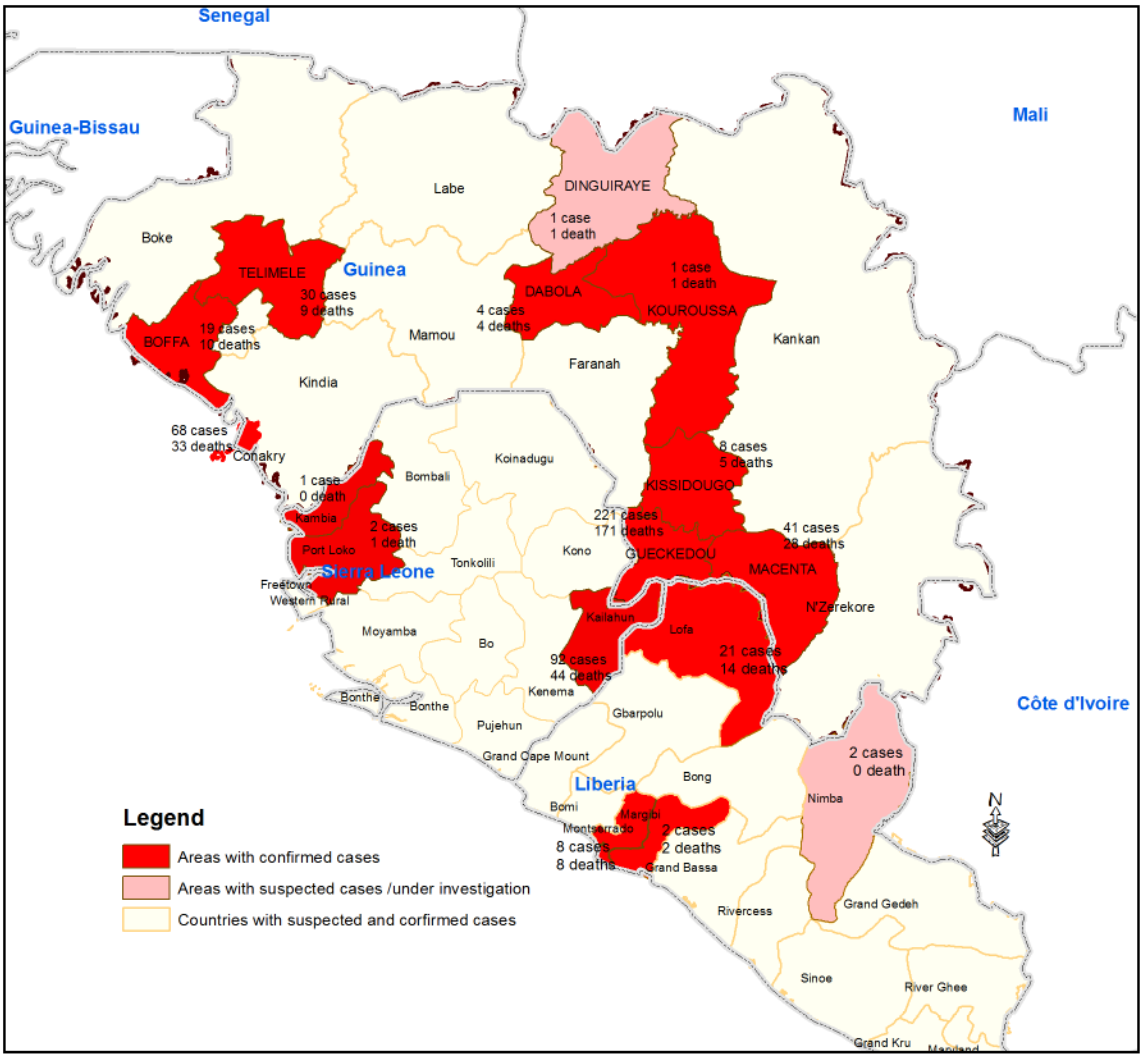
spread of infectious disease: people live in very tight quarters, many share the same bed and sanitation is relatively non-existent due to the dearth of running water, toilets or electricity (128).

On June 23, 2014, MSF released a statement declaring that the epidemic was out of control (146). The organization had reached their human capital limits and was unable to send more teams to new outbreak sites. They accused the WHO, civil, political and religious leaders of 'failing to acknowledge the scale of the epidemic' and shirking their responsibilities to curb the spread of the disease. By this point in time, MSF had treated 470 patients in Ebola Treatment Centers in Conkary, Telimele and Gueckedou (Guinea); Koidu, Daru, Buedu and Kaiahun (Sierra Leone); and Foya and JFK Hospital in Monrovia (Liberia). They were supporting the Ministries of Health of Liberia to conduct epidemiologic surveillance. As experienced as MSF was in treating patients and mounting outbreak control measures in Ebola zones, there were limits to what the organization could do on its own with the 300 staff they had working in West Africa. They faced human capital limitations and were having difficulties finding qualified state and international staff to treat and isolate patients, engage in contact tracing and mount awareness-raising activities in the community.

At the end of June 2014, there were 413 cases and 313 deaths in Guinea, 107 cases and 65 deaths in Liberia and 239 cases and 99 deaths in Sierra Leone for a total of 759 cases and 467 deaths among all three countries (147). The WHO pointed to the persistent failure in local communities to comply with recommended control measures for the accelerated resurgence of cases since May. In particular, the WHO cited the reluctance of patients to seek care in Ebola Treatment Centers and electing instead to be

cared for at home as the primary driver that was fueling household and community transmission of the virus. Cross border movement and traffic was also facilitating the wide geographic spread of the disease (148).

	Guinea			Liberia			Sierra Leone		
	Cases	Deaths	**% Δ cases**	Cases	Deaths	% Δ cases	Cases	Deaths	**% Δ cases**
March (131)	122	80	---------	8	2				
April (136)	218	141	**73%**	35					
May (140)	291	193	**37%**	Not available			50	6	----------
June (147)	413	303	**41%**	107	65		239	99	**378%**



Source: http://www.afro.who.int/en/clusters-a-programmes/dpc/epidemic-a-pandemic-alert-and-response/outbreak-news/4165-dashboard-ebola-virus-disease-evd-in-west-africa-16-june-2014.html

Figure Fourteen. This map shows the spread of Ebola in West Africa as of June 17, 2014. Active cases were detected not only in the rural areas of Guinea, Liberia, and Sierra Leone but also in the capital cities of Conkary, Monrovia, and Freetown. The WHO cited several reasons for the widespread transmission of disease (148):

1. Negative cultural practices that resulted in mistrust of public health messages, poor health care seeking behavior such as the hiding of patients, and traditional burial practices.
2. Extensive movement of people across borders;
3. Non-comprehensive containment procedures in the context of a weak health care infrastructure.

July 2014 The WHO convened a meeting in Accra, Ghana on July 2-3, 2014 to bring together the Ministries of Health from 11 countries (Côte d'Ivoire, the Democratic Republic of the Congo, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Senegal, Sierra Leone, and Uganda) as well as Ebola survivors, representatives of airlines and mining companies, and donor communities to analyze the situation in West Africa, to identify response gaps, to develop operational plans and to ensure increased political commitment and collaboration among countries. The objective was to "obtain consensus from Member States and partners represented on the optimal way of interrupting the ongoing Ebola virus transmission in West Africa to reduce the human, social and economic impact of the Ebola outbreak in West Africa for the current and future outbreaks" (148).

As a result of that meeting, on July 31, the governments of Guinea, Liberia and Sierra Leone and the WHO Regional Office in West Africa released the Ebola Virus Disease Outbreak Response Plan in West Africa (150). In it, the key players formally requested that the WHO in Geneva would 'lead and coordinate the international response to the outbreak.' Among other things, they asked the WHO to provide leadership in coordination of international partners; to mobilize staff, experts, and consultants; to assist with training health care professionals on how to prevent nosocomial transmission; and to facilitate cross and inter country collaboration. The document also recognized the challenges that the Ministries of Health faced in their efforts to control viral transmission, such as community participation, financial difficulties, cross border collaboration, and the inability to engage in the basic tenets of Ebola containment: infection prevention, isolation of patients, surveillance, and contact tracing. An operational plan based on

traditional outbreak protocols for controlling transmission was outlined and immediate actions included placing a response team in each hot spot, strengthening clinical supports and security along borders, isolating symptomatic patients, tracing of all contacts for 21 days, and distributing personal protective equipment supplies and materials. It was estimated that it would cost $100.5 million USD to control the outbreak (with a funding gap of $71 million USD) and the document beseeched the international community to donate additional human and material resources.

The WHO mobilized resources on the ground during the month of July. A sub-regional coordination center was set up in Conkary to implement the outbreak response and to identify and train community volunteers and supervisors (149). The local WHO offices in West Africa also began working with the Global Outbreak Alert and Response Network (GOARN), a collaboration of institutions and networks that combine human and technical resources to rapidly respond to outbreaks, to provide technical expertise and to support to the Ministries of Health of Liberia, Sierra Leone and Guinea in their efforts to control transmission of the virus (150). They deployed experts to work on surveillance and monitoring of the outbreak, to expedite laboratory confirmation of suspected cases, to isolate and treat patients, to dispatch and disseminate equipment and materials, and to train public health officials on contact tracing and the handling of Ebola cases.

The WHO worked directly with the Ministry of Health and Social Welfare of Liberia to identify and train 107 community volunteers and 33 supervisors. In Sierra Leone, 296 community volunteers had been trained and were sent into the field to conduct contact tracing and to evacuate suspected Ebola cases from the community (149). In addition, Gambia provided 11 health care workers to support the response in

Sierra Leone and the United States supplied personal protective equipment and other medical supplies (such as backpack sprayers and hand sprayers for disinfection as well disposal bags for biohazard wastes) to Liberia in order to ensure the safety of health-care workers (151).

As of July 24, 2014, MSF had 22 international and 250 local staff working in Sierra Leone and had trained an additional 200 community health workers to deliver health messages to people in their villages regarding self-protection and actions to take if one showed signs of the disease. In Liberia, MSF handed over the management of the Foya Ebola Treatment Center to Samaritan's Purse, a non-profit organization, and opened a tented treatment center with capacity for 50 beds in Monrovia. Caseloads in Guinea had been declining at a steady pace and MSF was winding down their activity in Conkary and closed their Ebola Treatment Center in Telimélé. Although cases in Gueckedou were declining, MSF opined that this did not necessarily reflect an end to the outbreak, rather it was reflective of the significant fear surrounding Ebola that caused infected people to hide in their homes. In response to this suspicion, MSF teams traveled to villages to find and treat patients who remained at home, but they were met with hostility and violence. Consequently, MSF began working with local authorities and elders to try to ensure safe access so they could obtain a clearer picture of the number of people hidden in villages and rural areas who were infected with and dying of the virus (154).

It wasn't until July 21, 2014 that Dr. Luis Sambo, the WHO Regional Director of the West African Region visited Guinea, Liberia and Sierra Leone to make a first-hand assessment of the outbreak, review the current response and to explore the best ideas and ways to control transmission of the virus (9). At the time of Dr. Sambo's tour, Guinea

reported 427 cases and 314 deaths; Liberia reported 249 cases and 129 deaths; Sierra Leone reported 525 cases and 224 deaths (a total of 1201 cases and 667 deaths) (152).

During his trip, Dr. Sambo held meetings with the Ministries of Health and non-governmental organizations and underscored the seriousness of the outbreak. He postulated that while Ebola could be contained using known infection control measures, the outbreak was at a scale such that control efforts exceeded the capabilities of any national health sector. He urged civil, societal and community responses to pool resources and work concurrently with national staff to end transmission of the virus (152).

Nigeria reported it's first case of Ebola at the end of July (152). On July 17, a Liberian national, who had been hospitalized in Monrovia as a suspected Ebola patient, checked himself out of the hospital and flew from Monrovia to Lagos, a city of 21 million people, on July 20. It was reported that he was visibly ill in the Monrovia airport and was lying on the floor at the departure gates. On the plane, which flew from Monrovia to Lagos via Accra, Ghana and Lome, Togo, he vomited several times and finally collapsed on the tarmac at the Lagos airport. He was immediately driven to a private hospital (the protocol officer who drove him later died from Ebola) where he told the attending physician he had malaria. He was unresponsive to malaria treatment and tested positive for Ebola. It was later discovered that his sister in Liberia was a confirmed case of Ebola and that he had visited her in the hospital and attended her funeral (154; 155).

The Liberian man, Patrick Sawyer, was working for, or traveling under the auspices of, the Liberian Ministry of Finance to attend a conference in Lagos.

Recollection of the chain of events that led to his departing Liberia vacillates: the Ministry of Health of Liberia contends that they unequivocally told Mr. Sawyer that he was not to travel because he was under observation. The then-Deputy Minister for the Budget, Sebastian Muah said he had authorized the trip despite Mr. Sawyer's condition, claiming medical ignorance. He later recanted that statement and contends that he never authorized his departure at all. Be that as it may, when Mr. Sawyer arrived at the hospital in Lagos, he was in such an agitated, and perhaps confused state, that he demanded he be released, even going so far as to seek the help of high-ranking Liberian officials, who allegedly pressured the hospital to release him so he could attend the conference. Mr. Sawyer died in Lagos on July 25 (154; 155; 156; 157).

Ebola spread outside of Lagos on August 1, 2014 when a direct contact of the Mr. Sawyer's in Lagos became ill and flew Port Harcourt to seek medical care from a private doctor. The doctor who treated him developed symptoms on August 10 and died on August 23 (154). During his travels while symptomatic, Mr. Sawyer reportedly exposed 72 people to the virus and from these, 898 peripheral contacts were identified. One hundred percent of the contact in Lagos and 99.8 percent of the contacts in Port Harcourt were followed up for 21 days, generating 18,500 visits. The outbreak was declared over in Nigeria on October 20, 2014; a total of 19 cases (nine of whom were health care workers) were identified and eight people died (154; 155; 156).

The spread of the virus in such a densely populated city such as Lagos could have been disastrous. However, it was the rapid, thorough and vigorous response by the Nigerian government that made containment so successful. An Incident Management

Center was established the same day that Mr. Sawyer was diagnosed, and all containment activities were organized and carried out from there.

It wasn't merely the establishment of the Center that accomplished the goal of eradicating of the virus. The Center, and the infrastructure that supported it, had been used to eradicate polio in Nigeria and those systems were reactivated to conduct contact tracing and to identify chains of transmission. Social mobilizers visited every house surrounding the homes of Ebola contacts, a total of 26,000 houses, disseminating information about the virus. All symptomatic or potentially symptomatic patients were immediately isolated for further testing and if confirmed, moved immediately to Ebola Treatment Centers (154; 155; 157).

Case Counts as of July 31, 2014

	Guinea			Liberia			Sierra Leone		
	Cases	Deaths	**%Δ cases**	Cases	Deaths	**%Δ cases**	Cases	Deaths	**%Δ cases**
Mar(131)	122	80		8	2				
April (136)	218	141	**73%**	35					
May (140)	291	193	**37%**	Not available			50	6	
June (147)	413	303	**41%**	107	65	_____	239	99	**378%**
July (158)	472	346	**14%**	391	227	**265%**	574	252	**140%**

August 2014 In the first few days of August, Dr. Margaret Chan, the Director-General of the WHO, held meetings with the Presidents of Guinea, Liberia, and Sierra Leone to review the status of the Ebola epidemic and create common strategies to eradicate the disease (63). On August 8, 2014, as there were 1779 cases and 961 deaths reported, the WHO declared that Ebola constituted a Public Health Emergency of International Concern (PHEIC)(159).

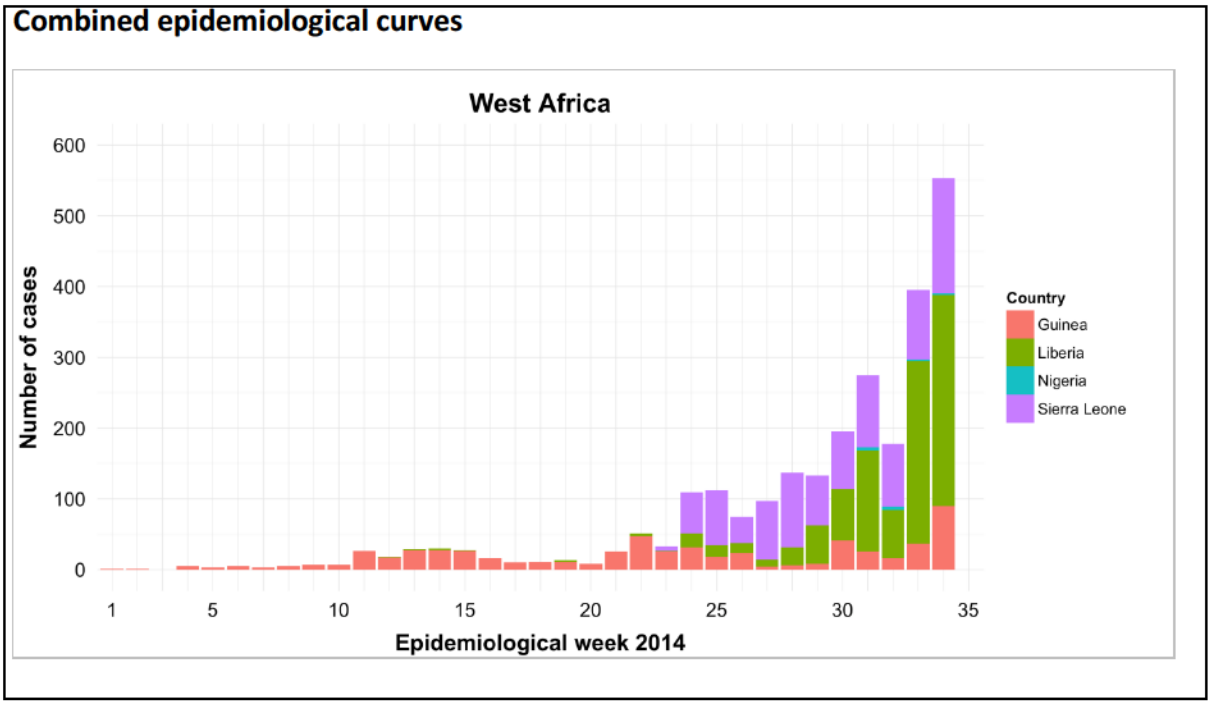
This declaration was not merely ornamental; it was an instrument of the International Health Regulations and represented a legally binding agreement made by 196 countries to contain major international threats (9). The consequences of such a declaration are immediate. In part, it decreed that Ebola affected countries should declare a national emergency, activate national disaster-management mechanisms and establish emergency operations centers. There were definitive expectations on constraining mobility across borders and within them. International travel of infected persons or their contacts was forbidden and the reduction of movement in areas of intense transmission was expected to be enforced.

The Agreement also contained recommended actions that affected countries were to implement in order to control the outbreak. These measures included directives on implementing control protocols such as contact tracing and monitoring. Local communities were to engage with religious and traditional leaders to provide information on the virus and how to prevent transmission. Infrastructure mandates included the distribution of personal protective equipment along with instruction on its proper use. Countries were also expected to provide clinical care and psychosocial support for all Ebola cases and to ensure that health care workers received timely payment of salaries

and hazard pay. Treatment centers were to be situated close to areas of transmission and have adequate numbers of trained staff and sufficient equipment to handle caseloads. There were also specific instructions that dictated that funerals were to take place in the presence of fully trained personnel while keeping families involved and respecting cultural practices. Finally, there were provisions for extraordinary measures, such as quarantine and lock-downs, to be implemented (159). Indeed, quarantine was implemented in August in all three West African countries; in October in Liberia in the Grand Cape Mount District (234; 235); in September in Sierra Leone when the Port Loko and Bombali districts were sealed off, restricting the movement of up to one million people (236). In the beginning of September, Sierra Leone enforced a three-day lockdown in which no one was permitted to leave their houses so the government could conduct house-to-house searches (169). In those three days, 7000 teams went door to door and identified 358 cases and uncovered 265 corpses (237; 238). In December, 2014 the northern part of Sierra Leone was under another quarantine and public celebrations of the Christmas holidays was banned (239); in late March 2015, Sierra Leone a second lockdown was implemented as officials tried to find cases and stem the spread of the virus (240). While these actions could be perceived as draconian, even as they are allowed under the declaration of the Public Health Emergency of International Concern, they are not coercive (9). Rather, it was expected that any and all measures were to be introduced with the understanding and collaboration of affected communities. Nonetheless, the quarantine in the West Point Slum of Monrovia in August 2014 ended in violence, clashes with the police, and the death of one 16 year old child (128; 161; 209).

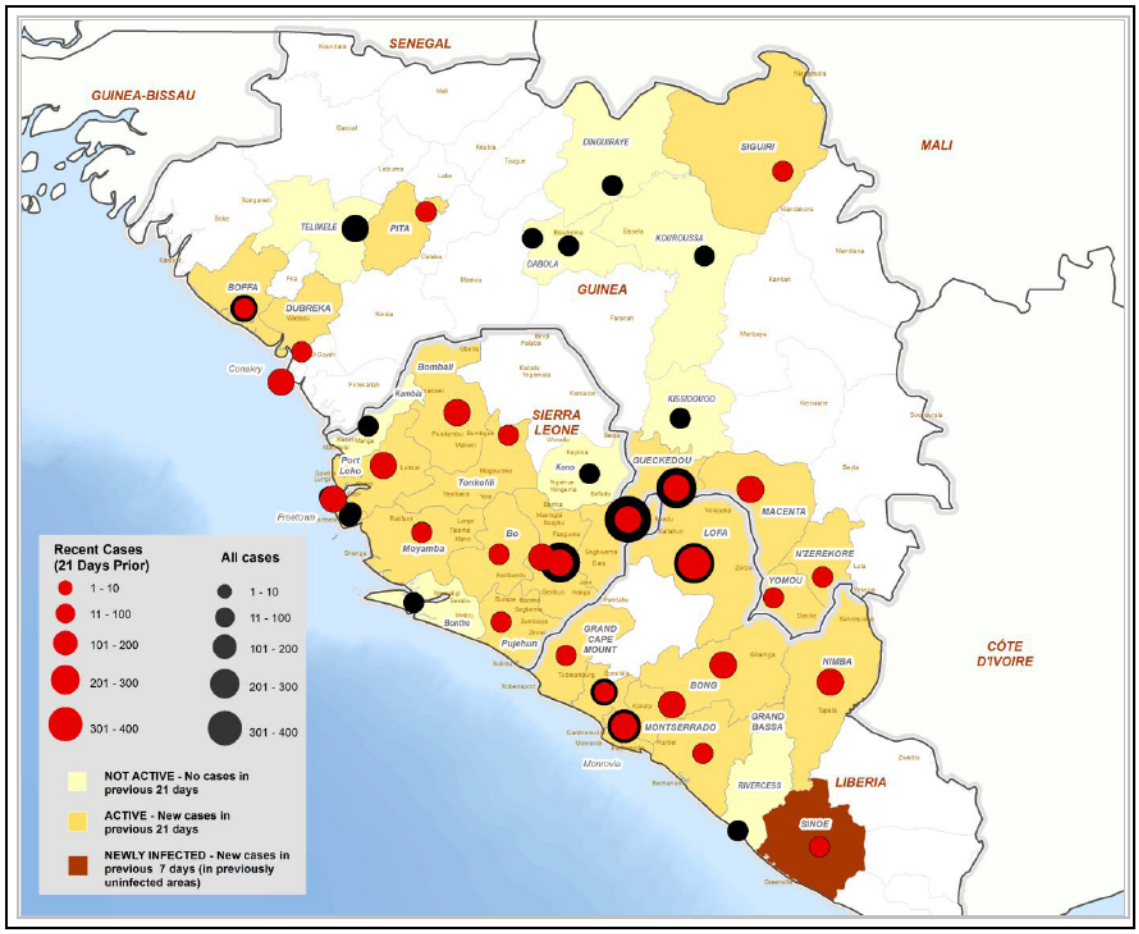
On August 28, a month after declaring the PHEIC, the WHO in Geneva released the Ebola Response Roadmap, a 20-page document in which the organization essentially took control of the outbreak response considering that "a massively scaled and coordinated international response is needed to support affected and at risk countries in intensifying response activities and strengthening national capacities" (162). The plan provided the backbone that sustained the response in West Africa and the action items contained therein would assist governments with country-specific operational plans. Nothing in the plan was necessarily revelatory or novel and most of the action items merely reiterated containment activities that were known to stop Ebola transmission. However, particular attention was paid to the necessity of training health care workers on the training of health care workers on the proper use of personal protective equipment and the mobilization, hiring and training of health care workers across the board to provide care in Ebola Treatment Centers.

Despite the fact that the WHO deployed 440 experts to the region, case totals in August were climbing. The Ministries of Health of Guinea, Liberia, Nigeria, and Sierra Leone reported an aggregate of 3475 cases and 1849 deaths; more than 40% of those occurring in the month of August alone. Of these, 257 were health care workers of whom 140 have died (164). During this time, assistance from governments within Africa began trickling in. South Africa and Senegal deployed mobile laboratories to Sierra Leone and Guinea. This was in addition to the labs provided by Canada, the Center for Disease Control and the Russian Federation (164).



Source:
http://apps.who.int/iris/bitstream/10665/131974/1/roadmapsitrep1_eng.pdf?ua=1

Figure Fifteen (164): While transmission had been steady and consistent throughout the summer of 2014, transmission appeared to cross the Rubicon on weeks 34 and 35 (the weeks of August 18 and August 25) when there was a large spike in cases in Liberia and to a lesser extent Guinea and Sierra Leone.



Source:
http://apps.who.int/iris/bitstream/10665/131974/1/roadmapsitrep1_eng.pdf?ua=1

Figure Sixteen (164): The spread of Ebola as of August 29, 2014. Sixty-two percent of the reported cases were found in Gueckedou, Guinea; Lofa, Liberia; and Kenema, Sierra Leone where transmission was first reported in each of the countries. Nine months after the beginning of the epidemic, transmission had not abated in the epicenters in each respective country.

Case Counts as of August 29, 2014

	Guinea			Liberia			Sierra Leone		
	Cases	Deaths	**%Δ cases**	Cases	Deaths	**%Δ cases**	Cases	Deaths	**%Δ cases**
Mar. (131)	122	80		8	2				
April (136)	218	141	**73%**	35					
May (140)	291	193	**37%**	Not Available			50	6	
June (147)	413	303	**41%**	107	65		239	99	**378%**
July (158)	472	346	**14%**	391	227	**265%**	574	252	**140%**
Aug(164)	648	430	**37%**	1378	694	**252%**	1026	422	**78.7%**

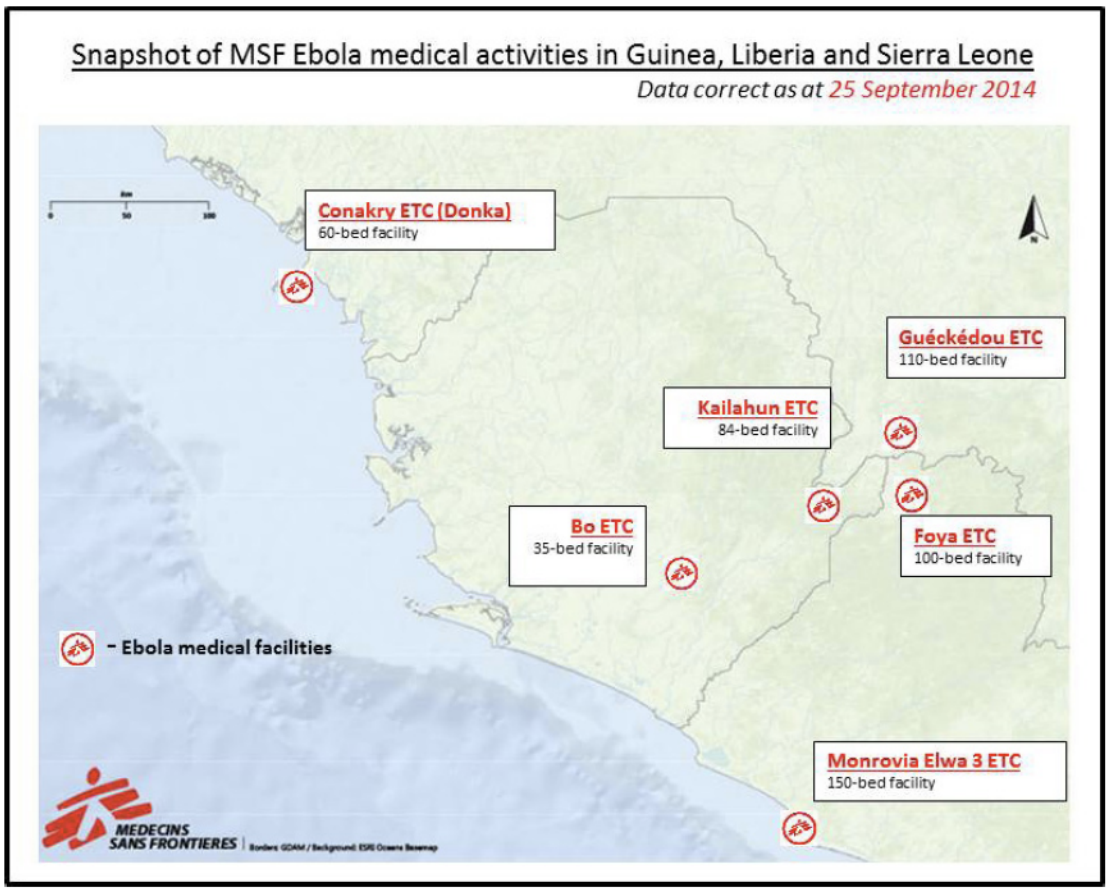
September 2014 By early September, MSF, frustrated with the dithering of the WHO and the non-existent international response to the epidemic, Dr. Joann Lui delivered a speech September 16 at a special briefing in Geneva of the UN Member States on the ebola outbreak and response in West Africa, in which she said she was "honestly at a loss as to how a single, private NGO [was] providing the bulk of isolation units and beds." On September 2, 2014, MSF International President Dr. Joanne Liu gave a speech to the United Nation member states in New York City and chastised the international community for failing to address the epidemic in a real and substantive way: "despite calls by MSF for a massive mobilization on the ground, the international response has been inadequate" and that "states have essentially joined a global coalition of inaction"(166).

The situation on the ground in West Africa deteriorated during the month of September. In one week alone, Liberia reported 400 incident cases and Sierra Leone reported 200 (167). The caseload in Liberia was primarily driven by a surge in transmission in the hotspots of Monrovia and to a lesser extent Lofa County, while the outbreak in Sierra Leone was mainly contained to Freetown, the Kenema and Kailahun Districts as well as Bo, Bombali and Port Loko. Guinea initially saw an uptick in cases

in the beginning of August in Conkary, Macenta and Gueckendou, but by the end of September transmission was reported as sustained yet moderate (167; 168).

The health care infrastructure continued to crumble under the weight of the increasing caseload. There were bed shortages in all three countries and even though national governments and international aid groups continued to build treatment centers, demand far outweighed supply. In the month of September, the Liberian government opened the 120-bed Island Clinic in Monrovia and a tented 40-bed Ebola Treatment Center in Bong County while the International Red Cross built a 60-bed treatment center in Kenema, Sierra Leone (169; 170). MSF built a new Ebola Management Center in Bo, Sierra Leone; ELWA3 in Monrovia; and a new facility in Foya. In total, MSF responded to the crisis with 258 international and 2800 locally hired staff who responded to the crisis in the field and provided care in six different Ebola Treatment Centers (170; 172).

By the end of September, the WHO reported that although there were 893 beds available for patients in Ebola Treatment Centers across the region, there was still a need for 2800 more (169). One of the obstacles to building more treatment centers was the disagreements between the Ministries of Heath and MSF regarding site selection in addition to the scarcity of qualified staff to run them (170).



Source: http://www.msf.org/article/ebola-crisis-update-sept-25th

Figure Seventeen: (172) By September 25, 2014, MSF reported that they had admitted 3299 patients since the beginning of the outbreak 650 of whom survived. The organization provided 549 beds across six Ebola Treatment Centers.

During September, financial pledges from the international community started coming in. On September 16, the United States of America committed to building 17 Ebola treatment centers (total capacity: 1,700 beds) in Liberia and to distributing 400,000 Ebola home health and treatment kits. The US military also planned to send approximately 3000 troops to train 500 health care workers a week (213). Cuba sent 150 medical personnel to Sierra Leone; China sent medical supplies and a field laboratory to

Liberia; France sent aid to Guinea while the United Kingdom pledged 700 beds in Sierra Leone (171).

Case Counts as of September 28, 2014

	Guinea			Liberia			Sierra Leone		
	Cases	Deaths	**%Δ cases**	Cases	Deaths	**%Δ cases**	Cases	Deaths	**%Δ cases**
Mar. (131)	122	80		8	2				
April (136)	218	141	**73%**	35					
May (140)	291	193	**37%**	Not Available			50	6	
June (147)	413	303	**41%**	107	65		239	99	**378%**
July (158)	472	346	**14%**	391	227	**265%**	574	252	**140%**
Aug(164)	648	430	**37%**	1378	694	**252%**	1026	422	**78.7%**
Sept (173)	1157	270	**78.5%**	3696	1639	**168%**	2304	884	**125%**

October 2014 (174; 175; 176; 177) Ebola transmission continued unabated throughout the month of October. After months of steady, but not an explosive number of new cases in Guinea, transmission became intense once again. The city of Conkary remained a key area of concern and the districts of Macenta, Kerouane, and Nzerekore reported the highest number of new cases. The latter two districts share a border with Cote D'Ivorie, which highlighted the need for increased border surveillance. The WHO reported that that there was a slowing of transmission in Gueckedou, where the outbreak began nearly a year earlier, but MSF described the situation much differently (182). They reported that more patients were admitted in October at their treatment centers than in the first eight months in operation. New cases were arriving every day in Gueckedou and 15 beds were added to accommodate demand.

While several districts in Guinea remained Ebola-free, the disease was spreading to virgin districts. New cases were reported in Beyla and Lola, both of which share a

border with Cote D'Ivorie; Kankan, which is on a major route to Mali and also on the border of Cote D'Ivorie; and Faranah, a district in the center of Guinea that shares a border with Sierra Leone. Boke, which resides in the Northern part of Guinea on the border of Guinea-Bissau, saw new cases of Ebola after a 21-day period of dormancy. Denial of Ebola and community resistance to humanitarian aid workers continued to be a problem in Guinea, and many families chose to keep suspected patients at home as a way to not only avoid treatment centers but also the mandatory cremation policy.

Conditions in Liberia were deteriorating rapidly and transmission was widespread. The Ministry of Health consistently reported that there were up to 400 new cases a week throughout the month. By the end of October the city of Monrovia had a decrease in weekly new cases, but the true picture of the state of the epidemic remained murky, primarily because it was suspected by the WHO and other aid groups that cases were being vastly underreported and that there were breaches in data collection. It was thought that in any given week the suspected case counts were in fact definite cases due to the delay in matching lab results with surveillance data.

Outside of Monrovia, the Liberian districts of Bong, Margibi, and Nimba (which shares a border with Cote D'Ivorie and Guinea) reported high transmission. After there were new cases reported in Grand Gadeh, every single district in Liberia had at least one case of Ebola. On the other hand, Lofa County, the district that reported the first cases in Liberia in Spring 2014, showed a consistent decrease in transmission.

The situation in Sierra Leone continued to get worse in October with over 400 new cases a week. Transmission in Freetown, Kenema, Kailahun, Port Loki, Bombali and Moyamba was so aggressive that the government imposed quarantine in an effort to

curtail the surge of new cases. Checkpoints were set up to prevent the one – two million people in the area from leaving the area. Surveillance systems were compromised and 85 percent of helpline calls were not getting a response. There were not enough ambulances to transport patients and symptomatic people attempted to make their own way to get care and often died in transit, putting others at risk. The Kailahun Ebola Treatment Center was receiving patients from adjacent districts such as Tonkilili (and eight hour journey), which left open the possibly of cross-contamination in ambulances or other forms of transport.

On September 18, 2014, the United Nations Security Council declared the Ebola outbreak in the West Africa "threat to international peace and security" and advised UN member states to provide more resources to fight the outbreak, which marked the first time the Security Council exercised its powers to intervene in a public health crisis. On September 19, 2014 the UN Mission for Ebola Emergency Response (UNMEER) was formed to address the epidemic and was tasked with coordinating the United Nations vast resources to combat the epidemic under the leadership of Dr. David Nabarro (214).

On October 1, the UNMEER rolled out a 90-day plan to control and reverse the epidemic, in which benchmark goals were delineated. The plan set 60 and 90 day goals: by December 1, 2014 (a 60-day target) the objective was to build enough treatment centers to isolate at least 70% of Ebola cases and have enough burial teams to safely bury at least 70% of patients. By 90 days, on January 1, 2015, the goal was to have capacity in place for the isolation of 100% of cases and the safe burial of 100% of patients, which was expected to result in an 85% decline in transmission in affected areas (174).

The need for beds continued to far outweigh supply. New Ebola Treatment Centers were slowly being built: two were erected in Guinea, six in Liberia and nine in Sierra Leone. MSF added a sixth 30-bed treatment center in Macenta that was run by the Red Cross and expanded capacity in Gueckendou by 15 beds (174). By the end of the month, 22% of the 4707 planned beds were built and 2110 more were earmarked for construction with a dedicated funding partner (175).

There were 140 safe burial teams in operation (24 in Guinea, 56 in Liberia and 50 in Sierra Leone) but nearly 400 more were needed to meet the UNMEER goal by December 1 (175).

Social mobilization campaigns increased in frequency and coverage during October. Guinea distributed hygiene kits to 71,000 households (486,000 people) (174); UNICEF reached 85,415 households (575,374 people) through door-to-door campaigns and has distributed over five million bars of soap and bottles of chlorine for hand washing and household water treatment since the outbreak began (241). MSF distributed 50,000 family protection and home disinfection kits in Monrovia (181). In Conakry, the United Nations Development Program (UNDP) mobilized a network of 2,500 young volunteers to distribute soap and chlorine and to teach community members how to thoroughly wash hands and to avoid contact with possible cases (242). UNDP also supplied hygiene kits containing 125 buckets, 420 bars of soap, and 50,000 information leaflets to the 30,000 members of the Sierra Leone Commercial Motorbike Riders Union to help reduce transmission. Known as Okada riders, these drivers pick up as many as 100 fares a day and are at high risk of Ebola infection due to the close contact they have with the people they transport (243).

Religious leaders delivered prevention messages in an estimated 7000 sermons across the country in over 12,000 mosques. Imams gave sermons, some as long as 30 minutes, about Ebola and how to protect oneself (177). A SMS campaign designed to coincide with the Festival of Tabaski delivered messages on hygiene practices. In Liberia, 50 radio stations, with the support from UNICEF, broadcast Ebola prevention messages to approximately 1.5 million listeners (175). Sierra Leone reached 1.5 million households in a house-to-house campaign (169).

Ebola in Mali (215; 216; 217; 218) October 2014 also saw the first Ebola case in Mali, when a two-year old little girl traveled from Beyla, Guinea while symptomatic, into Mali with her step-grandmother. A closer look at the sequence of events that led to the arrival of the virus in Mali is a good illustration, much like the first Nigerian Ebola case, of how one patient can expose hundreds of people to the virus across borders.

It started in the beginning of October when the two-year old's father, who was a Red Cross volunteer in a private medical clinic, became ill and died. He was not an officially known Ebola patient, but regardless of the cause of his illness, the people of Beyla believed that he was suffering from a bad-luck curse that was cast upon him following an argument with the village chief. Shunned from his peers, he retreated from Beyla to his native village of Sokodough, Guinea 143 km away, where he died on October 3, 2014.

In the meantime, back in Beyla, the man's mother fell ill and died of unknown causes on October 8. The next day, two of his (the father of the two-year old) brothers became ill, and after seeking treatment at a local hospital were transported to an MSF-run Ebola Treatment Center in Macenta. One of the brothers died en route and it is presumed

that the other died shortly after arriving at the ETC. Samples from both brothers taken post mortem came back positive for Ebola. A week later, the grandfather of the two-year old girl (and father of the three men who died) became ill himself, tested positive for Ebola, and died on October 20 in Gueckedou. At this point, the two-year old's father, two uncles, and grandfather were all dead. Her mother was still in good health.

The child's maternal step-grandmother arrived from Kayes, Mali to Beyes, Guinea to offer sympathies and returned to Mali on October 19 with her two-year old granddaughter, her other five-year-old granddaughter and her grown son (the children's uncle). Before their departure, the two-year-old was showing symptoms of Ebola: she had a high fever, cough, a bloody nose and bloody stools.

The party traveled by bus from Beyes, Guinea to Bamako, Mali where they disembarked and spent time visiting relatives in a household with 25 people. They then took another bus from Bamko to Kayes, Mali (Kayes has a population of 128,000 people and is located 600 km from the Malian capital of Bamko near the border of Mali and Senegal) where two traditional healers saw the child, one of whom took her to a nurse. This nurse suspected Ebola and took the child to Fousseyni Daou Hospital in Bamko where she was admitted on October 21. The preliminary diagnosis was malaria or typhoid (negative for the former and positive for the latter) but she did not respond to treatment. Lab results on October 23 came back positive for Ebola, at which point she was treated in isolation. The two-year-old girl died on October 24.

One hundred and eight contacts of the child were identified, 79 of whom were in the hospital, including 33 health care workers. These numbers do not include the contacts

of her paternal dead relatives in Guinea, all of whom were either confirmed or probable Ebola patients.

The Malian and WHO response was swift, thanks in part to WHO and CDC staff already on the ground in the country to implement prophylactic Ebola preparedness measures. They immediately began tracing contacts, isolating and monitoring suspected contacts, and implemented education campaigns on transmission risk and the imperative to seek immediate medical help for suspected cases. Existing public health infrastructure in Mali that were previously established by the US National Institutes of Health Tuberculosis and HIV projects further aided the country in its ability to rapidly respond to the outbreak. At the time of this writing, no other contacts associated with the two-year old girl have been documented as falling ill or dying from Ebola.

Case Counts as of October 31, 2014

	Guinea			Liberia			Sierra Leone		
	Cases	Deaths	**%Δ cases**	Cases	Deaths	**%Δ cases**	Cases	Deaths	**%Δ cases**
Mar. (131)	122	80		8	2				
April (136)	218	141	**73%**	35					
May (140)	291	193	**37%**	Not Available			50	6	
June (147)	413	303	**41%**	107	65		239	99	**378%**
July (158)	472	346	**14%**	391	227	**265%**	574	252	**140%**
Aug(164)	648	430	**37%**	1378	694	**252%**	1026	422	**78.7%**
Sept (173)	1157	270	**78.5%**	3696	1639	**168%**	2304	884	**125%**
Oct (179)	1667	1018	**44%**	6535	2413	**76.8%**	5338	1510	**132%**

Clinical Features and Epidemiologic Parameters of West African Outbreak (180)

Nine months into the epidemic, The WHO Ebola Response Team conducted a well-powered analysis of the epidemiologic parameters that defined the outbreak, which has heretofore been impossible because past outbreaks have occurred sporadically and in remote, resource limited settings. The data set included medical record information and clinical data from 4507 probable and confirmed Zaire Ebola cases that occurred from December 30, 2013 – September 14, 2014 in Guinea, Sierra Leone, Liberia, Nigeria and Senegal.

In concordance with past Zaire Ebola outbreaks, the most common symptoms upon presentation to a medical facility were: fever (87.1%), fatigue (76.4%), loss of appetite (64.5%), vomiting (67.6%) and diarrhea (65.6%) (Table Two). Demographically, the majority of the patients (60.8%) were 15 – 44 years old and equal in number with respect to gender. Patients who were 45 years or older had a higher risk of death (Odds Ratio 2.47, 95% Confidence Interval 1.79 – 3.46). Most of the symptoms common to Ebola infection were not statistically significant risk factors** for death, such as fever, fatigue, headache, vomiting and diarrhea. However, symptoms that were statistically significant indicators of death such as chest pain, cough, hiccups, difficulty swallowing and breathing, confusion, coma or unconsciousness, and hemorrhagic symptoms generally occur late in the course of a typical Ebola infection. Data and anecdotal information from past Ebola outbreaks indicate that once a patient begins to exhibit these symptoms they will most likely die.

**For the purposes of this paper, I defined statistically significant as those parameters in which the 95% confidence interval did not cross the null. Odds ratios were adjusted for country.

Table 1. Demographic Characteristics and Signs and Symptoms in Confirmed and Probable Ebola Case Patients with a Definitive Clinical Outcome in Guinea, Liberia, Nigeria, and Sierra Leone.*

Variable	All Patients	Patients Who Died	Patients Who Recovered	Odds Ratio (95% CI)†
		no./total no. (%)		
Demographic characteristics				
Male sex	685/1415 (48.4)	515/1056 (48.8)	170/359 (47.4)	0.93 (0.73–1.19)
Age group				
<15 yr	190/1378 (13.8)	145/1021 (14.2)	45/357 (12.6)	1.18 (0.83–1.71)
15–44 yr	838/1378 (60.8)	577/1021 (56.5)	261/357 (73.1)	0.48 (0.36–0.62)
≥45 yr	350/1378 (25.4)	299/1021 (29.3)	51/357 (14.3)	2.47 (1.79–3.46)
Health care worker	158/1429 (11.1)	112/1067 (10.5)	46/362 (12.7)	0.86 (0.60–1.27)
Signs and symptoms				
General symptoms				
Fever‡	1002/1151 (87.1)	746/846 (88.2)	256/305 (83.9)	1.34 (0.92–1.95)
Fatigue	866/1133 (76.4)	633/829 (76.4)	233/304 (76.6)	0.94 (0.68–1.28)
Loss of appetite	681/1055 (64.5)	498/778 (64.0)	183/277 (66.1)	0.92 (0.69–1.23)
Vomiting	753/1114 (67.6)	566/816 (69.4)	187/298 (62.8)	1.19 (0.89–1.59)
Diarrhea	721/1099 (65.6)	555/813 (68.3)	166/286 (58.0)	1.42 (1.06–1.89)
Headache	553/1035 (53.4)	407/757 (53.8)	146/278 (52.5)	1.03 (0.78–1.36)
Abdominal pain	439/992 (44.3)	311/715 (43.5)	128/277 (46.2)	0.85 (0.64–1.13)
Muscle pain	385/990 (38.9)	293/728 (40.2)	92/262 (35.1)	1.24 (0.92–1.67)
Joint pain	374/950 (39.4)	283/695 (40.7)	91/255 (35.7)	1.32 (0.98–1.80)
Chest pain	254/686 (37.0)	196/488 (40.2)	58/198 (29.3)	1.53 (1.07–2.20)
Cough	194/655 (29.6)	150/462 (32.5)	44/193 (22.8)	1.74 (1.18–2.61)
Difficulty breathing	155/665 (23.3)	123/472 (26.1)	32/193 (16.6)	1.68 (1.10–2.63)
Difficulty swallowing	169/514 (32.9)	138/375 (36.8)	31/139 (22.3)	2.22 (1.41–3.59)
Conjunctivitis	137/658 (20.8)	109/465 (23.4)	28/193 (14.5)	2.03 (1.29–3.29)
Sore throat	102/467 (21.8)	82/339 (24.2)	20/128 (15.6)	1.94 (1.13–3.46)
Confusion	84/631 (13.3)	68/446 (15.2)	16/185 (8.6)	2.00 (1.14–3.71)
Hiccups	108/947 (11.4)	91/699 (13.0)	17/248 (6.9)	2.15 (1.27–3.82)
Jaundice	65/627 (10.4)	52/443 (11.7)	13/184 (7.1)	1.83 (0.99–3.63)
Eye pain	48/622 (7.7)	39/438 (8.9)	9/184 (4.9)	1.95 (0.95–4.40)
Rash	37/642 (5.8)	30/453 (6.6)	7/189 (3.7)	1.90 (0.86–4.83)
Coma or unconsciousness	37/627 (5.9)	34/445 (7.6)	3/182 (1.6)	4.59 (1.61–19.34)
Unexplained bleeding	168/932 (18.0)	140/693 (20.2)	28/239 (11.7)	1.83 (1.20–2.90)
Hematemesis	26/670 (3.9)	20/503 (4.0)	6/167 (3.6)	1.07 (0.44–3.01)
Blood in stool	48/843 (5.7)	35/614 (5.7)	13/229 (5.7)	0.98 (0.52–1.96)
Bleeding gums	19/837 (2.3)	18/608 (3.0)	1/229 (0.4)	6.69 (1.35–121.32)
Bloody nose	16/836 (1.9)	15/610 (2.5)	1/226 (0.4)	8.02 (1.54–148.62)
Bloody cough	20/831 (2.4)	16/605 (2.6)	4/226 (1.8)	1.63 (0.58–5.82)
Other bleeding	8/657 (1.2)	5/493 (1.0)	3/164 (1.8)	0.45 (0.11–2.23)
Bleeding at injection site	20/833 (2.4)	19/605 (3.1)	1/228 (0.4)	6.51 (1.32–118.04)
Blood from vagina§	14/431 (3.2)	13/290 (4.5)	1/126 (0.8)	6.0 (1.11–112.4)
Blood in urine	10/827 (1.2)	9/601 (1.5)	1/226 (0.4)	5.14 (0.90–98.73)
Bleeding under skin	5/827 (0.6)	5/604 (0.8)	0/223	NA

* Data are as of September 14, 2014. Patients with date of onset up to August 17, 2014, were included. Total numbers are the numbers of patients with data on the variable in question. NA denotes not applicable.
† Odds ratios are adjusted for country. CI denotes confidence interval.
‡ Fever was defined as a body temperature above 38°C; however, in practice, health care workers at the district level often do not have a medical thermometer and simply ask whether the person's body temperature is more elevated than usual.
§ Percentages reflect only female patients.

Source: http://www.nejm.org/doi/full/10.1056/NEJMoa1411100#t=article

Table Two: (180) Demographic characteristics and disease signs and symptoms of 4500 Zaire Ebola patients in West Africa who were treated from December 30, 2013 – September 14, 2014. Most of symptoms were not statistically significant risk factors for death, expect those that are normally seen in the final stages of disease pathogenesis. While the risk of death was essentially equal between genders, older patients did have a significantly higher risk of death.

The mean incubation period (the time between initial exposure to the virus and the onset of symptoms) was 11.4 days. This parameter can be used as a proxy for the amount of time contact tracers have to properly identify and quarantine patients in the community who could have possibly been infected with Ebola. The mean time from onset of symptoms to hospitalization was 5.0 +/- 4.7 days, which is a measure of the period that any given patient is infectious in the community. Once admitted, patients who died did so after 4.2 days of hospitalization and those who survived were discharged 11.8 days later, statistics that are reflective of other outbreaks.

The Case Fatality Rates were 64.3% among *hospitalized* patients with a known clinical outcome and 70.8% among *all patients* with a known clinical outcome. However, this statistic is only as reliable as the data it comes from: in order for patients to be included in the analysis they had to survive long enough to get to a treatment center. They not only had to obtain transportation to the treatment centers (and by all accounts, ambulance service in West Africa during the height of the outbreak was unreliable at best), but also they had to actually be admitted to the center to be counted. There was a well-documented shortage of beds during most of the outbreak, leaving many patients to either wait and die, literally in treatment center doorways, or they returned home to die. It is likely that many patients, including those who were the most seriously ill and simply couldn't physically make it to a center, died quickly and before they could obtain proper care, meaning that the true case fatality rate could be higher than these rates calculated.

A few parameters that were not accounted for in this analysis were the quality of health care, the type of treatment received or the ratio of patients to doctors at the time of admission. Various papers have illustrated, and was discussed earlier in this paper, that

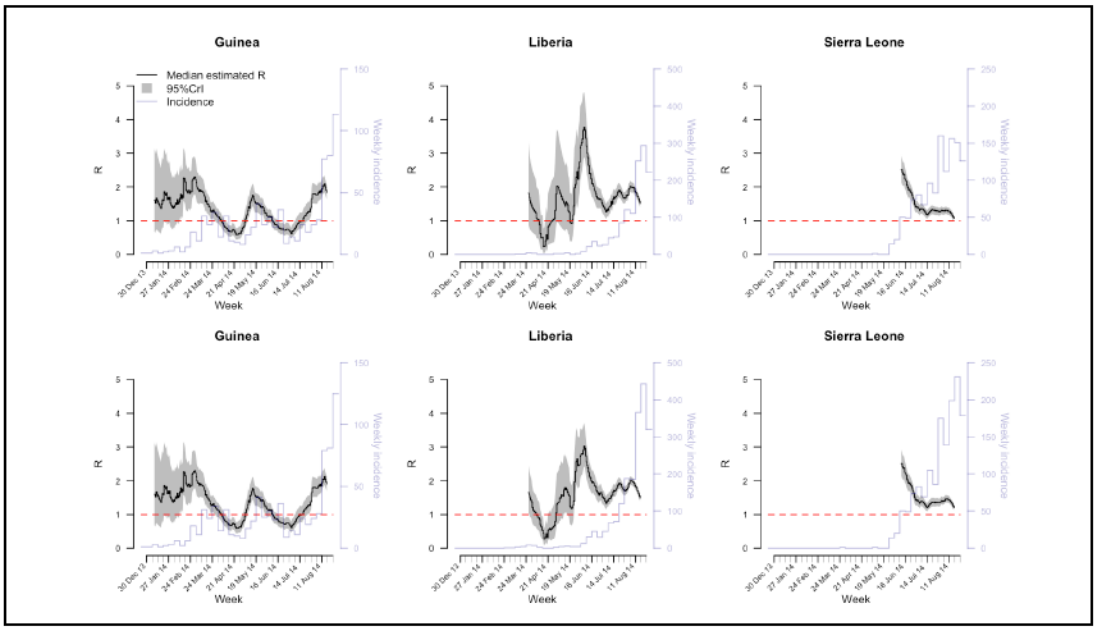
administering Oral Rehydration Therapy and maintaining electrolyte levels is imperative to ensuring positive patient outcomes. It is also reasonable to assume that those who sought care earlier in the outbreak may have better care and more positive outcomes than those who received care later in the outbreak when facilities were overwhelmed with patients. Likewise, although the mean time from symptom onset to hospitalization was measured, it was not held constant in the odds ratio calculations. It would be informative to measure risk factors for death between patients who sought and received care immediately upon symptom onset as compared to those who waited a five days or longer.

The basic reproduction number (Ro), a measure of the number of people who will be infected by one sick person in a population solely made up of susceptible patients, was calculated as 1.71 in Guinea; 1.8 in Liberia; and 2.02 in Sierra Leone. The net reproduction number (R(t)) for the period of July 28 – September 7 measured at 1.81 for Guinea, 1.51 for Liberia and 1.38 for Sierra Leone. The integrity of the reproductive number is dependent upon accurate and thorough reporting of cases. Considering that substantial underreporting of cases has been problematic in this epidemic; the true reproductive number may indeed be higher.

While the R(o) is a static measure and indicative of the infectiousness of a pathogen, R(t) is a dynamic variable that illustrates the negative relationship between the length of an epidemic and the Basic Reproduction Number. In the long term, R(t) will decrease as the number of survivors increases (assuming that survivors have immunity to re-infection) and the number of susceptible people decreases. When the value dips below one, the epidemic cannot be sustained and it will eventually burn out. However, in the short term, it is to be expected that R(t) will actually rise at the beginning of an epidemic

while there is heavy transmission and before infection control procedures can be implemented. As time passes and as community adherence to infection control practices are more closely observed, it is expected that R(t) will decrease. Indeed, in West Africa there has been a variation of R(t) over time with clear spikes and valleys that coincide with an increase of reported Ebola cases (Figure 18).

This is particularly noticeable in Liberia where a ban on traditional burial practices was implemented and repeated messages were delivered regarding transmission control and the imperative of seeking proper care in an Ebola Treatment Center. Conversely, in Guinea it has been widely acknowledged by the WHO and MSF that there has been, and continues to be, strong resistance to Ebola Response Teams; a systematic refusal to accept that Ebola is real; and the perpetual hiding of infectious patients. This resulted in a decrease of reported cases, which is shown in the R(t) graphs. This dip did not actually represent a decrease in transmission. When the number of cases hidden away reached critical mass, and the virus reemerged once again, case counts and the R(t) likewise rose.



Source: www.nejm.org/doi/suppl/10.1056/NEJMoa1411100/suppl_file/nejmoa1411100_appendix1.pdf

Figure Eighteen (10): The WHO Estimates of the reproduction number (Rt) over 4-week period, by country and by week of symptom onset. The top row is based on confirmed and probable cases, the bottom row is based on confirmed, probable and suspected cases. The dip of R(t) below one in April coincides with the drop of reported cases, which indicated that the outbreak was waning and could not be sustained. It is now known cases and their contacts were hiding from epidemiological surveillance out of fear and that transmission was still in fact occurring at a rather rapid rate. In early May, as these cases began to emerge, R(t) rose again.

Data from another set of 106 Ebola positive patients in Sierra Leone who were treated from May 25 – June 18, 2014 showed similar results (139). Of these 106 patients, 44 had a known outcome and an associated clinical chart. At presentation, 89% of these exhibited fever; 80% had headache; 43% were vomiting; and 61% had diarrhea. Statistically significant factors for death were diarrhea, weakness, dizziness, and age above 21 (see Table Three). In addition, of patients who had a known outcome (N=87), 63 had initial viral load measurements were taken by means of RT-PCR. The results

show that those who had more than 10 million copies of virus per milliliter of serum had a statistically significant higher risk of death than those who presented with less than 100,00 copies of virus (Table Four). While the viral load measurements were taken at time of presentation to the Kenema Government Hospital, how long each patient had been infectious was not factored into the calculations. For example, it is not clear if patients who had higher viral loads upon arrival actually waited longer to seek care (the mean time to seek care after onset of symptoms was 5.7 +/- 0.5 days in this study), which has been shown to be a risk factor for death. It is impossible to disentangle whether it was waiting to seek care or if it was viral load upon presentation that is the true risk factor for death. Furthermore, it has been argued by some scientists that viral load is not a predictor of death since at the beginning of an Ebola infection, viral load is generally the same between fatal and non-fatal cases. If this is true, then the ability for one person to survive over another may come down to genetic factors, underlying health conditions or the qualitative and quantitative measures of care. Therefore, perhaps viral load at presentation could be used as a proxy measurement for the risk of death in waiting to seek care.

	Fatal	Not Fatal	Total	Odds Ratio	PValue
Diarrhea	17	1	18	**6.27**	P<.05
No Diarrhea	19	7	26	1.00	
Total	36	8	44		

	Fatal	Not Fatal	Total	Odds Ratio	PValue
Weak	22	1	23	**11**	P <.01
Not Weak	14	7	21	1.00	
Total	36	8	44		

	Fatal	Not Fatal	Total	Odds Ratio	PValue
Dizzy	20	1	21	**9.18**	P<.01
Not Dizzy	16	7	23	1.00	
Total	36	8	44		

Table Three: (146) Statistically significant risk factors of death among 44 patients who had complete medical charts and observed outcomes. All patients presented to the Kenema Government Hospital in Sierra Leone between the days of May 25 – June 18, 2014. Measurements and symptoms were recorded upon presentation. Those who presented with diarrhea had 6.27 times greater odds of death than those who did not exhibit such symptoms. Patients who reported feeling weak had 11 times greater risk of death than those who did not report feeling weak. Those who complained of dizziness had a nine times greater odds of death than those who were not dizzy upon arrival. While these results are interesting, they are hampered by a small N and are not particularly powerful.

To calculate the odds ratio in Table Three and Table Four I used the numbers of fatal and not fatal patients according to risk factor and/or clinical symptoms that were provided in the Supplementary Appendix of the paper. The Pvalues were provided in the text of the paper.

source:www.nejm.org/doi/suppl/10.1056/NEJMoa1411680/suppl_file/nejmoa1411680_appendix.pdf

	Fatal	Not Fatal	Total	Odds Ratio	PValue
Age Under 21	13	10	23	1.00	
Age 21 – 45	35	12	47	**2.2**	
Age Over 45	15	1	16	**11.5**	P = .03
	63	23	86		

	Fatal	Not Fatal	Total	Odds Ratio	PValue
<10^5	5	10	15	1.00	
10^5 – 10^7	23	7	30	**6.56**	
>10^7	17	1	18	**34**	P <.001
	45	18	63		

Table Four: Age was shown to be a statistically significant risk factor for death with those who were over the age of 45 showing a 11.5 times greater risk of death. Likewise, those patients who had viral loads of greater than 10 million copies per milliliter of serum had 34 times greater odds of death than those who had loads of less than 100,000 copies at presentation.

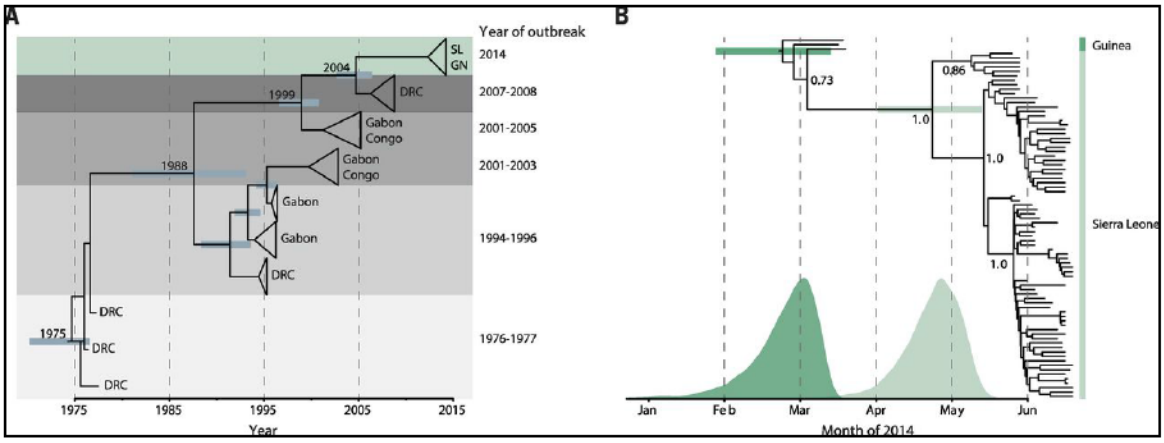
A limited number of patients also had viral loads measured longitudinally throughout their hospitalization and the results indicated that it was the inability to clear the virus, regardless of viral load upon presentation that was a risk factor for death. This inability could be related to several different factors discussed in the pathogenesis and immunology section of this paper.

Phylogenetics of West African Outbreak (183; 184) As previously discussed, cases of Zaire Ebolavirus had not been recorded in West Africa before 2014 and it is unclear as to how or why the virus appeared 3000 km (approximately 2000 miles) away from its presumed natural home in Central Africa. Phylogenetic analysis of the Ebola strain found in West Africa provided some evolutionary evidence as to the history of the virus and how closely related it was to Ebola strains of outbreaks past. Genomic sequencing of viral isolates from 78 confirmed Ebola patients in Sierra Leone revealed that the current epidemic arose from a variant of the Zaire Ebolavirus that diverged from Central African strains within the past decade (around 2004).

The phylogenetic tree on the left hand side of Figure 19 represents a tree that was constructed using Ebola strains from past outbreaks as well as those taken from the 78 Sierra Leone patients as well as three patients from Guinea. The 2014 strains form their own clade but share a common ancestor with the strains isolated from the 2007 outbreak in the Democratic Republic of Congo. The separation of the Sierra Leone and the Guinea strains into a different clade supports the theory that the 2014 outbreak did not spread from a currently infected person in Central Africa, but rather that the genesis of this outbreak was most likely the result of an independent zoonotic event. While it has been argued that an infected person could have become infected in Central Africa and then traveled to West Africa, this seems unlikely (10). If typical modes of transportation were utilized, it could take up to a week to travel between these two parts of the continent. Considering the time period from initial exposure to Ebola to death, it is nearly impossible for an infected person to travel from Central Africa to Guinea within the confines of the disease pathogenesis, be infectious upon arrival, and able to transmit the

virus. Furthermore, genetic similarities across the 2014 samples, which are illustrated in the horizontal distance between each of the variants, imply that only one spillover event sparked the outbreak and that subsequent spread of the disease has been sustained through human-to-human transmission.

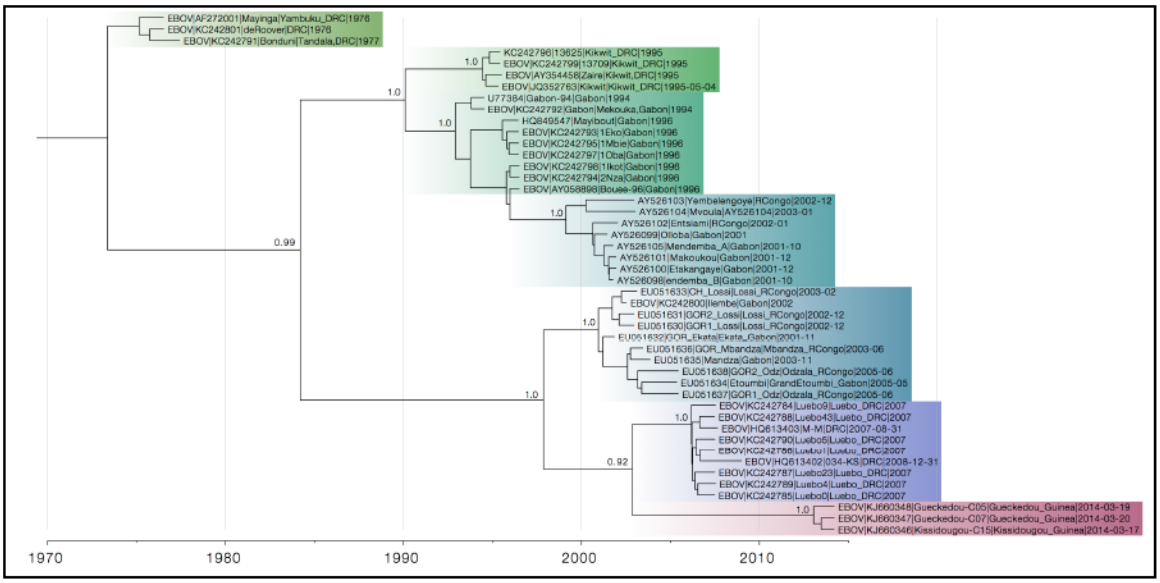
The tree on the right hand side of Figure 19 is a tree that was constructed solely using the strains isolated from patients in Sierra Leone and Guinea. The tree shows that the outbreak started in Guinea in March and went through a few mutations as transmission increased. The tree also appears to show that although the strains found in Sierra Leone are genetically descended from the Guinea strain, there are two separate clades, perhaps three, which suggests that there were two strains circulating in Sierra Leone. This supports a theory that there that there were two distinct viruses introduced into Sierra Leone from Guinea within a couple of months of each other.



Source:
www.sciencemag.org/content/early/2014/08/27/science.1259657.full?explicitversion=true

Figure Nineteen (183): Phylogenetic tree of 78 confirmed Ebola patients in Sierra Leone who were diagnosed from late May to mid-June and three laboratory confirmed Guinean samples. The tree to the right shows that the Sierra Leone and Guinea strains are on separate branches but within the same clade. Outbreak strains that are the most phylogenetically similar to the 2014 strains are those that were found in the 2007 outbreak in Luebo, Democratic Republic of Congo, which is housed in its own clade. The nearest common ancestor of the two clades is dated to about 2004, when there was a divergence in the Zaire Ebolavirus strains.

The tree to the left shows a Beast generated tree of only the 2014 strains. The three Guinea strains are very closely related and the spread of the disease into Sierra Leone is clearly marked. Within the Sierra Leone variants, there are two separate clades, which indicates that there were two genetically distinct viruses introduced into the country from Guinea. All subsequent diversity in the Sierra Leone variants are descended from these two viruses.



Source: currents.plos.org/outbreaks/article/phylogenetic-analysis-of-guinea-2014-ebov-ebolavirus-outbreak-2/

Figure Twenty (184): A phylogenetic tree containing the three Guinea strains along with strains from past outbreaks as well as strains taken from apes that perished in the Lossi Sanctuary in 2002. In concordance with the tree constructed in Figure 20, the 2014 strains form their own clade and share a nearest common ancestor with the strains found in the Democratic Republic of Congo in 2007. Posterior probabilities indicate that there is 92% certainty that the strains diverged from one another around 2004.

Zoonotic Reservoir of West African Outbreak The zoonotic reservoir for the Ebolavirus has never been definitively identified and it was thought that perhaps non-human primates that tested positive for Ebola RNA might be the reservoir host. Several human Ebola outbreaks have been associated with the handling and consumption of infected mammal carcasses (most frequently chimpanzees) and there have been documented epidemics in non-human primate communities that occurred concurrently with human outbreaks. However, all evidence that has been collected and observed with respect to Ebola pathogenesis in non-human primates suggests that they, like humans, develop symptomatic and fatal infection. This would point to their role as an intermediary or dead-end host, rather than the reservoir (187; 189).

Bats, on the other hand, have stronger evidence to support the hypothesis that they may be the reservoir host. In 1996, lab experiments proved that bats infected with Zaire Ebolavirus were able to replicate virus, mount an adaptive immune response and survive without showing signs of overt infection (187). In 2002, during a post-outbreak investigation, Ebolavirus RNA was detected in three different fruit bats that lived in the Gabonese forest (189). In 2005, viral RNA sequences were found in the liver and the spleen of three different kinds of fruit bats, none of which exhibited symptoms: Hypisignathus Monstrosus, Epomops Franqueti , and Myonycetris Torquata. While IgG antibodies to Zaire Ebolabvirus were found in these species of bats as well, neither RNA nor IgG antibodies were found at the same time. Although nucleotide sequences were found in the bat specimens, scientists were not able to isolate the virus itself (186; 187). The index case in the 2007 outbreak in Luebo, Democratic Republic of Congo was reported to have contact with freshly killed bats in a market just prior to falling ill with a

mild case of Ebola (54). All of these findings give weight to the hypothesis that bats are the natural reservoir host of the Ebolavirus, however, none proves it beyond a reasonable doubt. The strongest evidence that has implicated bats as the reservoir host was in 2007 when Marburgvirus was isolated from the fruit bat Rousettus Aegypticus (188, 190).

The exact mechanisms of bat immunology is not entirely understood, but it is believed that bats can maintain an asymptomatic state while sustaining viral replication and mounting an adaptive immune response (with a corresponding helper TCell activation) that clears the infection. While some believe that bats only shed virus while under active viral replication, others have hypothesized that bats maintain a chronic, active viral state and that shedding occur in spatial pulses during times of immunologic stress related to food scarcity or pregnancy (185).

With respect to the spillover event that started the 2014 outbreak (123), all that was known was that the index patient was a two-year-old boy in Meliandou. No hard data had been collected regarding any exposure he may have had to bats or other intermediate hosts. There was not any evidence that suggested a decline in non-human primate or mammal populations in the forests surrounding Meliandou, that wasn't explained by hunting or migration, prior to or concurrently with human transmission of the virus in December.

Operating under the assumption that the two-year old boy from Guekendou was the index case and that he was exposed to the virus from either the natural reservoir or intermediate host, a team of scientists spent four weeks in April 2014 in Meliandou looking for data that could shed some light as to the nature of the primary spillover event. The goal for the expedition was to locate the zoonotic reservoir, to ascertain if there had

been widespread wildlife decline prior to the outbreak, and to study human behaviors and practices associated with hunting bats and other wildlife.

The team did not find that there had been a decline in local wildlife populations either concurrently with or prior to the outbreak in Meliandou, leading researchers to believe that handling of wild game or bushmeat was not the spillover culprit. In this area of Guinea, most large game that is consumed is not hunted locally, rather it is brought in from areas in the northwestern part of the country. While this does leave open the possibility that the imported meat was infected, this is not likely. Even had wild life been infected with Ebola, the index case would have most likely been one of the hunters or a person who bought and prepared the meat for consumption, not a two-year-old child.

Fruit Bats, on the other hand, are hunted and consumed locally. Local bat hunting is primarily the responsibility of the patriarch of the family, who hunts with a gun, nets or his bare hands. Bats are generally hunted in forest patches or caves surrounding Meliandou and the catch is either sold at market or burned in a fire to be used for meat in sauces. Children also hunt and capture bats with their friends as a form of amusement, but do so in a different manner than adult hunters. They find bats in hollow trees or under thatched rooftops and use a stick or their hands to directly catch them or knock them to the ground. The species of bats that are hunted for food are different than those bats that are hunted for amusement by children; hunters target fruit bats while children aim at insectivorous bats.

The investigating team was able to capture and sacrifice 13 species of bats representing six different bat families (they captured 88 bats in Meliandou, 20 in Kagbadou, four in Kelema and 57 in Zaima) in the area including and surrounding

Meliandou, three of which (Eidolon Helvum, Hypsignathus Monstrosus and Mops Condylurus) were found serologically or RT-PCR positive for Ebolavirus, although no viral RNA was detected and tests for Ebolavirus IgG antibodies were inconclusive. This does not prove that the bats are the reservoir and it certainly does not prove that bats in the area at the time of the spillover event were infectious or shedding virus. All it means is that at the time of the research, bats were found to have either Ebola antibodies or fragments of virus in their bodies.

Through interviews with local villagers and observations of the topography of the land surrounding the village, researchers did discover a hollow tree located 50 meters from the home of the index patient. This tree was known to be the residence of a colony of bats as well as a playground for children, including the index patient. Researchers were not able to examine the tree or capture any of the bats that resided in it. On March 24, 2014 as the epidemic grew and authorities issued warnings about the dangers of consuming bushmeat, the tree was burned down. There are conflicting stories as to the rationale for burning the tree. Some villagers reported that the tree was burned because of the bushmeat ban, others say that the tree was burned during a botched attempt to extract honey and yet other stories indicate that the tree was burned accidentally by children who were playing with fire.

Regardless of how or why the tree was burned, there are consistent reports that a 'rain of bats' emerged from the tree as flames consumed it and a large number of these bats perished in the fire. Those bats were collected by residents of Gueckendou with the intent of consumption, but they were discarded the next day after the official ban on bushmeat was announced. RNA sequencing analysis from ash samples and soil around

the base of the tree indicated that Mops Condylurns bats, also known as the insectivorous Angolan Free Tailed Bat, inhabited the tree.

The results of this investigation into the potential zoonotic reservoirs in Gueckendou did not uncover any evidence that handling of diseased intermediate hosts was the cause of the outbreak. Likewise there was no evidence that implicated adult hunting and consumption of bats as the zoonotic event. No hunters resided in the household of the index patient and had the spillover been tied to consumption, the person who handled the bats during hunting and/or preparation would have been the index patient, which was not the case in this outbreak.

The only epidemiologic evidence uncovered in Gueckedou with respect to possible zoonotic reservoirs and the two-year-old child was the hollowed out tree and the bats that resided in it, but nothing discovered in the investigation could implicate bats in that tree as the zoonotic source. Given anecdotal evidence about bat handling behaviors in the village and the elimination of other sources of spillover normally attributed to Ebolavirus outbreaks, it is possible that the zoonotic event could be related to the Mops Condylurns bats residing in a hollow tree where the index patient played, but it is far from conclusive. It seems highly unlikely that a two-year-old child would be old enough or dexterous enough to engage in the hunting of bats, however it is possible that he could have been exposed to the virus while playing in the tree or he might have played with an already-dead infected bat or ingested a small quantity of infected bat droppings.

Discussion

On March 25, 2015, nearly one year after Ebola was identified in West Africa, there have been 24, 907 reported cases of Ebola and 10,326 deaths (98). For a brief moment in the spring of 2014, as recorded case counts declined, the WHO and the Ministries of Health believed that the outbreak would naturally burn out, as all other outbreaks in the past had done (137). That prediction did not come to pass. Transmission continued unabated both within Africa and across international borders ever since, making this Ebola outbreak the largest ever recorded. There are several reasons as to why this outbreak has become the largest in history and has failed to respond to historically effective transmission control efforts.

1. Coordination and Leadership Issues The first and foremost reason is that a centralized, robust and international response was not implemented immediately. The WHO failed to acknowledge the seriousness of the virus and its potential to spiral out of control during the first few critical months of the epidemic. Lost opportunities were fueled by structural issues within the WHO itself and weaknesses in the organization.

In past Ebola outbreaks, once Ebola was identified, local WHO offices and Ministries of Health communicated openly with WHO and immediately requested the deployment of international teams of experts to control viral transmission. In the Uganda Sudan Ebolavirus outbreak in 2000, Ebola was identified as the causative agent on October 15, 2000, and the very next week the Ministry of Health requested that the WHO coordinate the international response (101). In the Gabon Zaire Ebolavirus outbreaks from 1994 to 1996, the Gabonese health authorities requested the intervention of Centre

International de Recherches Médicales de Franceville (CIRMF) two weeks after a cluster of deaths from an unknown cause were reported. The CIRMF team identified Ebola in that outbreak and was in the area to assist in implementing control measures for the next two outbreaks that occurred over the next two years, both of which were contained relatively quickly resulting in comparably few deaths (98; 99). In Yambio, Sudan a cluster of deaths from an unknown cause was reported on May 6, 2004; the WHO and the Kenya Medical Research Institute conducted an initial investigation on May 9, 2004; Ebola was detected from patient samples on May 16, 2004; and on May 19, 2004 a first-response team made up of members from the WHO's South Sudan Early Warning and Response Network and the WHO headquarters in Geneva was dispatched to the field to support local health authorities (192). During the Mekambo outbreak in 2001, it took only eight days after Ebola was verified from patient samples for a response team comprised of members from the Gabonese Ministry of Health, the WHO headquarters in Geneva and partners from The Global Outbreak Alert and Response Network (GOARN) to be dispatched to the field (100; 193). In Luebo, Congo in 2007, approximately one month after Ebola was detected, the Democratic Republic of Congo Ministry of Health, MSF, and the WHO headquarters in Geneva formed an international response team that investigated and controlled the outbreak (54).

The only outbreak that did not have a timely response from the WHO was in Kikwit, Congo in 1995 (96). The outbreak investigation began in May, three months after cases started to present at local hospitals and five months after the first case was detected in January 1995. The initial investigation was to assess if the putative cause of death was dysentery, which added another six weeks delay in determining that patients were in fact

dying of Ebola. However, once Ebola was confirmed, an international team was formed in 48 hours and was sent to the field to interrupt viral transmission and to reestablish confidence in the health services. The team included experts from the WHO, the CDC, Institute of Tropical Medicine, MSF, South African Medical Institute, the International Red Cross, and Institut Pasteur.

In the West Africa outbreak, the WHO West African Regional Office was tasked with guiding control efforts on the ground, deploying personnel to affected regions, and supporting the efforts of Ministries of Health (124). However, rather than appointing Dr. Pierre Formety, the WHO's top Ebola authority as the coordinator of the response team, the West African office chose an official from the Guinea WHO Office who had never before been involved in an Ebola outbreak (3).

Locally, the Guinean, Liberian and (eventually) Sierra Leone Ministries of Health activated national and district emergency management committees to search for and manage cases; to trace contacts; and to educate communities on transmission (124; 127). They distributed Personal Protective Equipment, medical supplies, and trained health care workers on the Ebola itself and infection control (125). Their main partner on the ground was MSF (124, 168) who established an Ebola Treatment Center and was actively isolating and treating patients, while the WHO reported that they were "closely monitoring the need for logistics in affected areas and building capacity on the ground to stop transmission" (137).

Local efforts were inadequate to control the spread of the disease. On May 27, 2014, two months after Ebola specific containment efforts began, there were 281 reported cases and 176 deaths and the virus had spread to the Guinean capital of Conakry, the

Liberian capital of Monrovia and into Sierra Leone (138; 126; 140; 141; 142). To put it in perspective, number of cases and deaths at this time were edging upon those that were seen in some of the largest outbreaks recorded. Of the outbreaks mentioned in this paper that received international support, the final case counts were: 315 cases and 250 deaths in Kikwit, 425 cases and 224 deaths in Uganda, 149 cases and 97 deaths in Gabon during 1994-1996, 17 cases and seven deaths in Yambio, 65 cases and 53 deaths in Mekambo, and 32 cases and 15 deaths in Luebo (18; 122).

Throughout the balance of May and into June, the WHO reported that they were continuing to develop response plans and held regular meetings at the national levels to review the situation and to propose control measures. In early July, there was a sub-regional Ministerial meeting in Accra, Ghana to address solutions for ending the outbreak. On July 18, 2014, when there were 1048 cases and 632 deaths (151), the WHO was still reviewing the outbreak responses, developing plans and identifying response. By the end of July, the WHO West African Office, along with the governments of Guinea, Sierra Leone, and Liberia, finally understood that their ability to stem transmission had failed and officially asked the WHO in Geneva to coordinate the response and to take over control efforts. Approximately a week later, the WHO declared the outbreak a Public Health Emergency of International Concern (9; 159), but it wasn't until August 28, 2014 that the WHO released the Ebola Response Roadmap (164), which laid out an official plan to stop the virus from spreading. By this time, local health systems were overwhelmed and the virus had spread to the point where it was beyond being contained with available resources. The window of opportunity to control the outbreak in an expedient manner and minimize morbidity and mortality had closed.

2. Mobility and Urban Paradigms An important concern unique to this outbreak is the mobility of the people in West Africa, particularly in the area where the outbreak began, and the consequent spread of the virus to urban centers (10). Gueckedou is located where the borders of Guinea, Sierra Leone and Liberia converge and major road networks there allow people to travel across the porous borders to patronize markets, visit family and to participate in shared socio-cultural practices (102; 148; 208). As mentioned earlier in this paper, it is believed that the initial Liberian case was a woman who contracted the virus in Guinea when she patronized a market there (126; 207). The primary cluster of cases in Sierra Leone was traced back to border movement after a group attended the funeral of a traditional healer in Guinea, became infected themselves and then returned to Sierra Leone (138). The first cases in the Monrovia, Liberia and Conakry, Guinea traveled from rural areas via public transportation, creating multiple opportunities for high-risk exposure during the journey (207; 3).

The geographical range of the 2014 outbreak was peculiar to this epidemic. Most outbreaks in the past were confined to remote settings of limited population that by definition allowed for a certain degree of containment (196). This gave public officials a controlled environment to engage in standard response protocols such as contact tracing, patient isolation, and quarantine. In West Africa, the virus spread almost immediately into Liberia and Sierra Leone, making the outbreak area span thousands of square miles. Once infected individuals eventually landed in capital cities, they were impossible to trace and the outbreak became impossible to control (195).

3. Community Factors

After Ebola was identified, governments began to disseminate informational messages about the virus itself and how to control transmission. However, there was an inherent distrust in the government and public health messages with respect to Ebola. This skepticism of the government to act in the best interest of its people meant that citizens assumed that they were being lied to and that Ebola wasn't real (244).

Consequently, Ebola treatment teams were stonewalled when they tried to administer care in rural communities. The Red Cross estimated that their teams in the field have been attacked, on average, 10 times a month (197). MSF reported that one of their facilities in Guinea was attacked when locals heard a rumor that the organization had brought Ebola with them (199). Vehicles were vandalized and equipment was seized and publically burned. In Macenta, riots erupted because it was believed that an infection control team that was spraying chlorine was actually spraying the disease. The riot grew to almost 3000 armed people and caused the team to literally run for their lives (4). Villagers close to the city of N'zerekore used machetes and clubs to kill a team made up of local officials, health-care workers, and journalists who were traveling from village to village trying to raise awareness about the disease (198). The problem still continues: it was reported on February 15, 2015 that crowds destroyed an Ebola facility and attacked health care workers in Faranah, Guinea after locals discovered that the Red Cross was planning to disinfect a school (219).

This type of fear in the face of such a deadly disease is not a novelty or particular to West Africa. In the very first Ebola outbreak in Zaire in 1976, villagers in Yambuku were incredibly terrified and agitated. The team that responded to the outbreak reported

that they were able assuage those fears by explaining to villagers what was known about the disease and how they intended to stop it. By all accounts, the villagers were eventually responsive, particularly when house-to-house visits included local clinicians (52; 94).

The historical political paradigm that exists in West Africa is different than in 1976 Zaire, but nonetheless, there was an acceptance of help and willingness to do what was necessary to control the outbreak 38 years ago that was missing in 2014. It is difficult to know if the approach of the Ebola response teams in West Africa was different compared to Zaire. Regardless, the messages delivered in 2014 were ignored and fought against and this helped to spread the disease. It seems that the problem was noticeably more challenging in Guinea, but the lack of acceptance, and the hesitancy to seek proper care and to abstain from high-risk practices was found in all three West African countries (148; 174).

There was some headway made by the governments at the local level to establish trust and foster cooperation. In Guinea, representatives from the Ministry of Health and senior government officials worked with 23 village leaders who agreed to embrace the parameters of the Ebola outbreak response and to work within their communities to encourage compliance (200). In Sierra Leone, the 149 Paramount Chiefs (grass roots leaders bound to their communities by tradition and familial ties) committed to visiting households in their chiefdoms to check on health statuses and to educate people on the symptoms of Ebola and how to protect oneself. The Bumpeh Chiefdom in particular was very aggressive, setting up 200 hand washing stations, visiting every household every day and setting up 50 checkpoints to monitor movement both in and out of the chiefdom.

Also in Sierra Leone, the head of traditional healers in one district agreed to stop treating patients suspected of having Ebola (201).

There was also hesitancy on the part of patients to seek proper care, which fueled community transmission of the disease, because there was misunderstanding and fear of what happened inside the treatment centers. It was whispered in villages that Ebola patients disappeared after they entered a treatment unit, never to be seen again and that their bodies would be "thrown away." There were rumors that patients did not actually receive care at all and that they were not fed. It was believed that entering a treatment center was tantamount to death. Dying from Ebola is a profoundly lonely and isolating experience and it was thought better by many to remain at home and die amongst loved ones rather than in a frightening center surrounded by doctors in 'white space suits' (245).

While these rumors had no basis of truth to them, there were others that did. Many people did not want to seek treatment because they did not want to be known as the house or the family that had Ebola. The stigmatization of Ebola patients and their families in local communities and neighborhoods is very real. There is unkind gossip and social isolation. They are forbidden from using local wells, selling food at community markets, or attending religious services.

As a result, relatives hid symptomatic family members and tried to escape the surveillance system, causing more transmission and death. Ebola "refugees" were known to flee infected towns to hide with family and friends in rural communities (4; 194). The numbers bear this out. Since late July 2014, the International Federation of Red Cross and Red Crescent Societies has been responsible for majority of the collection and the

cremation of all dead bodies from Ebola Treatment Centers in most of Liberia. For the period July 28–October 26 they reported that a total of 2,234 bodies were collected, the majority of which (1,179; 53%) were taken from homes or other community settings, and only 744 (33%) from Ebola Treatment Centers, 194 (9%) from other health facilities, and 117 (5%) from unknown locations (202).

The fact that most corpses were picked up in communities and not Ebola Treatment Centers indicate that there was indeed a problem of patients hiding in the home and that the epidemic was and is most likely much worse that what is reported by the WHO in their Situation Reports. The WHO acknowledges underreporting and confirms that there is and was deterioration in the ability of overwhelmed responders to record accurate data. Liberia in particular has had a difficult time reconciling data management, and it is believed that the number of actual cases in the West Africa region were twice as much (a Correction Factor of two) than what was being reported (203).

4. Health Care Infrastructure

Ebola Treatment Center Supply and Demand As cases increased and Ebola spread, the weak health care infrastructure buckled under the weight of trying to manage and properly isolate Ebola patients. As the number of Ebola admissions in hospitals increased and more and more health care workers became ill and died, those who remained healthy were afraid to provide care and simply did not come to work. Some hospitals simply collapsed under the combination of the strain of too many patients and not enough staff to care for them. Many hospitals and clinics closed including JFK, the largest hospital in Liberia, which shut down in July for two months after several of its prominent doctors

died of Ebola. Many of those that remained open refused to treat patients with Ebola-like symptoms.

In order to properly treat and isolate the rising number of Ebola patients, MSF, international organizations and foreign governments scrambled to build Ebola Treatment Centers, but there was still a dearth of beds. As of January 14, 2015 (246), only 38% of the required beds (250 out of 655) were available in Guinea, 26% of the required beds (510 out of 1989) were available in Liberia and 68% of the required beds (1207 out of 1783) were available in Sierra Leone. Not only was there a shortage of beds, but also there was a shortage of qualified medical staff to care for patients, so even as centers were built they were understaffed, which meant that patients were not receiving optimal care. The supply-demand disequilibrium meant that sick patients remained waiting, sick and infectious, outside of the center doors, where they often died or they returned home where they spread the disease to family members or anyone with whom they had close contact.

Post Civil War The West African region had only recently emerged from years of conflict and civil war, which destroyed or disabled many sectors of the economy, including the heath care infrastructure. The Civil War in Sierra Leone lasted from 1991 – 2002 and left the country with 70,000 dead, 2.6 million people displaced and nearly every hospital established by the government destroyed. During the war, many doctor and nurses fled the country, leaving the citizens to literally fend for themselves (204). In Liberia, where the civil war lasted from 1989 – 2003 (with a couple of intervening years of peace) the situation was much the same. The war left a near destruction of 242 out of the 293 health

care facilities. Most of the doctors and nurses left, leaving the country with 30 doctors for three million people (205). Although Guinea did not find itself in its own civil war, the country was pulled into the Liberia conflict when the Revolutionary United Front (RUF) attacked Guinea on at least two occasions in 2000 and 2001, which left large-scale damage, killed thousands of people, and displaced over 250,000 Guineans (240).

The number of physicians per 1000 people is an indication of the availability of health care in the event one becomes ill. In Sierra Leone and to a lesser extent Liberia, the number of doctors in the country dwindled during the civil wars. As the epidemic expanded and deaths mounted, health care workers were a part of that statistic. By February 11, 2015, there were 830 health care workers infected and 488 of them died.

Physicians per 1000 people

	1990	1996	1997	2000	2004	2005	2008	2010
Guinea	.134			0.094	0.11	0.1		0.1
Liberia			0.023		0.03		0.014	0.014
Sierra Leone		0.073			0.03		0.016	0.022

Source: http://data.worldbank.org/indicator/SH.MED.PHYS.ZS

In contrast to the doctor : population ratio in West Africa, the United States there is an average of 2.5 doctors per 1000 people; the United Kingdom has 9.4 doctors per 1000 people; in Switzerland there are 11.3 doctors per 1000 people; and Norway has 9 doctors per 1000 people.

Infrastructure Spending Expenditure on health as a percentage of GDP**,** a measure of both public and private health expenditures and indicative of the strength of the health care infrastructure, also suffered because of the Civil Wars. The percentage spent in Sierra

Leone dipped to 16% during the conflict, and only rose two percentage points after the war; in Liberia, only 6% was spent during the height of the war, but has risen to almost 20% in 2011. While the United States consistently spends approximately 18% of GDP on health care; the United Kingdom 9.4%; Switzerland 11.3%; and Norway 9%, the GDP among these countries are very different from those in West Africa. Even though the percentage spent is around the same, actual monies allocated are much less in West Africa. Additionally, money spent to maintain a functional system, such as that in the United States, is very different that monies distributed to repair broken or non-existent systems. The dichotomy is particularly noticeable in Sierra Leone and Liberia where the economies dipped precipitously after the civil war ended. Interestingly, the GDP of Guinea did not suffer from a loss of national income and has had marginal growth.

Expenditure on health care as a percentage of GDP

	2000	**2005**	**2010**	**2011**
Liberia	5.9	8	16.4	19.5
Guinea	5.7	5.4	6.2	6
Sierra Leone	17.5	16.1	20.8	18.8

Source: http://data.worldbank.org/indicator/SH.XPD.TOTL.ZS

GDP in Current USD

	1990	**2000**	**2005**	**2010**	**2013**
Switzerland	2.57E+11	2.71E+11	4.07E+11	5.81E+11	6.85E+11
UK	1.06E+12	1.54E+12	2.41E+12	2.40E+12	2.65E+12
Guinea	2666616177	2995360969	2937072009	4735956476	6144131903
Liberia	384400000	529064646	542000000	1292696476	1950960138
S.Leone	649644826	635874002	1627853086	2578159496	4136280752
US	5.97E+12	1.02E+13	1.30E+13	1.49E+13	1.67E+13

Source: http://data.worldbank.org/

Health Indicators Longitudinal measures of health care indicators, which could be construed as an effect of the functionality of a health care system as well as markers of overall public health, reveal that during the war years infant and maternal mortality declined, but remain some of the highest in the world, even a decade after the war ended. Incidence of tuberculosis was down in Guinea but has increased in both Liberia and Sierra Leone during and after the Civil Wars. While immunization rates have risen somewhat over the 23 year span represented here, the rates are still short of what is necessary for what is required for herd immunity. It should be noted that poor countries with a weak infrastructure, or those that are in the middle of a war, might not have the most reliable surveillance and data collection systems. It is entirely possible that the numbers reported to the World Bank by Guinea, Liberia, and Sierra Leone are not representative of what was happening in these countries with respect to public health.

Percentage Children Under Age Five Immunized Against DPT

	1990	1995	2000	2005	2010	2013
Guinea	17	54	46	59	64	63
Liberia			46	60	70	89
S. Leone			44	65	86	92

Source: http://data.worldbank.org/indicator/SH.IMM.IDPT/countries

Percentage Children Under Age Five Immunized Against Measles

	1990	1995	2000	2005	2010	2013
Guinea	35	61	42	51	58	62
Liberia			63	62	65	74
S. Leone			37	71	81	83

Source: http://data.worldbank.org/indicator/SH.IMM.MEAS/countries

Incident Tuberculosis per 100,000 people

	1990	1995	2000	2005	2010	2013
Guinea	249	250	228	210	186	177
Liberia	199	220	240	267	293	308
S. Leone	252	282	305	316	317	313

Source: http://data.worldbank.org/indicator/SH.TBS.INCD/countries

Maternal Mortality (Deaths per 100,000 women)

	1990	1995	2000	2005	2010	2013
Guinea	1100	1000	950	800	690	650
Liberia	1200	1600	1100	880	680	640
S. Leone	2300	2400	2200	1600	1200	1100

Source: http://data.worldbank.org/indicator/SH.STA.MMRT

Infant Mortality (Deaths per 1000 live births)

	1990	1995	2000	2005	2010	2013
Guinea	238	206	170	137	112	101
Liberia	248	229	175	118	82	71
S. Leone	268	256	232	202	175	167

Source: http://data.worldbank.org/indicator/SH.DYN.MORT/countries

The Human Development Index (http://en.wikipedia.org/wiki/Human_Development_Index) is a measure of the prosperity of a nation that includes physical, educational, and economic health indicators. The tool was developed by Indian economist Amartya Sen and Pakistani economist Mahbub ul Haq in 1990 and has since been used by the United Nations as the country level measure of social and economic development. It is based on four criteria: life expectancy at birth, mean years of schooling, expected years of schooling and gross national income per capita. The calculation ranges from 0, indicating that a country has negligible human development to 1, indicating that a country has very high human development.

Below are the listed measures for Sierra Leone, Guinea and Liberia. The 2013 ranks are the latest official measurements available and countries are listed out of 187, which means that the West African countries have the lowest human development in the world, even before the Ebola outbreak.

Human Development Index

	1990	2000	2005	2010	2012	2013	2013 Rank	HDI Δ from 2012
Liberia		0.339	0.335	0.393	0.407	0.412	175	3
Guinea			0.366	0.38	0.391	0.392	179	-2
Sierra Leone	0.263	0.297	0.329	0.353	0.368	0.374	183	0

Source: http://hdr.undp.org/en/data

The Education Index A more direct and specific portrait of the educational status of a nation is measured by the Education Index, which is also published by the United Nations Development Program. It is calculated using two variables: mean years of schooling (years that a 25-year-old person or older has spent in schools) and expected years of schooling (years that a 5-year-old child will spend with his education in his whole life).

A value of 1 is the highest possible theoretical score, indicating that a country has achieved perfect educational attainment. The scores in West Africa, listed below, have been consistently low over the past 25 years, with marginal improvements being made. By way of comparison, in 2013 the United States has a score of .89, the United Kingdom: .86; Switzerland: .84; and Norway: .91.

It is thought that the lack of education in West Africa has contributed to the spread of the outbreak, particularly with respect to the unwillingness to heed the warnings by the government and international aid organizations about the seriousness of Ebola, the imperative of seeking care, the adherence to protection measures, and behavior modifications that could prevent transmission (226).

Education Index: Calculated using mean years and expected years of schooling

	1980	1990	1995	2000	2005	2010	2013
Guinea					0.253	0.2861	0.29445
Liberia	0.1703	0.2644	0.3121	0.344	0.349	0.3672	0.3672
Sierra Leone	0.1639	0.1827	0.2215	0.274	0.286	0.296	0.3045

Source: http://hdr.undp.org/en/content/education-index

Multidimensional Poverty Index (MPI). MPI is an index of poverty that uses a multidimensional model to measure the number of deprivations with which poor households typically contend (source: http://hdr.undp.org/en/content/multidimensional-poverty-index-mpi).

A person is considered poor if they are deprived in at least a third of the weighted indicators and the following ten indicators are used to produce the measurement (source: http://en.wikipedia.org/wiki/Multidimensional_Poverty_Index):

1. Years of schooling: deprived if no household member has completed five years of schooling.
2. Child school attendance: deprived if any school-aged child is not attending school.
3. Child mortality: deprived if any child has died in the family.
4. Nutrition: deprived if any adult or child is malnourished.
5. Electricity: deprived if the household has no electricity.
6. Sanitation: deprived if the household's sanitation facility is not improved (according to UN Millennium Development Goals guidelines), or it is improved but shared with other households
7. Drinking water: deprived if the household does not have access to safe drinking water or safe drinking water is more than a 30-minute walk from home round trip.
8. Floor: deprived if the household has a dirt, sand or dung floor.
9. Cooking fuel: deprived if the household cooks with dung, wood or charcoal.
10. Assets ownership: deprived if the household does not own more than one radio, TV, telephone, bike, motorbike or refrigerator and does not own a car or truck.

The intensity of poverty denotes the proportion of indicators in which they are deprived. For example in Liberia, those who are poor suffer from deprivation in 81.9 % of the indicators. In Guinea, the poor suffer from deprivation in 86.5 % of the indicators and in Sierra Leone, the poor are 72.7% deprived.

Percentage of the Population with a weighted deprivation score of at least 33% in 2013

	2013
Liberia	81.9
Guinea	86.5
Sierra Leone	72.7

Source: hdr.undp.org/en/content/table-2-human-development-index-trends-1980-2013

5. Broken Chains of Containment Protocols Containment of Ebola is an intense process that is dependent upon sound epidemiologic surveillance measures, which in turn rely on a large investment in human capital to work properly. Containment protocols exist in a continuous loop: infected patients and suspected cases must be isolated in a proper facility; there must be a methodical and consistent process to trace and monitor every single contact of every single case for 21 days; contact tracers should be trained to recognize and measure Ebola symptoms in contacts; all suspected and probable cases found among the contacts who are traced need to have their medical condition properly assessed and their disease status confirmed by rapid laboratory tests; and finally, all confirmed infected contacts must be isolated in a treatment center and every single one of their contacts must be monitored for 21 days. With every new case detected amongst the contacts, the cycle must be activated once again (220).

This cycle of surveillance is impossible if cases are being un-reported. By definition, these unrecorded cases include unrecorded contacts (4; 173; 221). Any breach in any part of the chain of surveillance can exacerbate the epidemic: a single missed case or a single missed contact who contracts the disease can start another chain of transmission (223). The integrity of the relationship between epidemiologists and Ebola

patients and their contacts must be preserved to stop an Ebola epidemic and this balance is dependent upon a functioning outbreak control system.

The reality is that outbreak protocol and the containment systems necessary to control an Ebola epidemic did not exist in West Africa. In a Perspective column in the New England Journal of Medicine, a nurse working at an Ebola Treatment Center in Kailahun, Sierra Leone reports that 250 contacts identified were identified in one week, but given the number of confirmed cases, there should have been closer to 1500 contacts (222).

Of the Ebola patients that were accounted for, the task of following up their contacts was a monumental one (4; 173, 174; 221). Many contact tracers reported evasion on the part of contacts, some of whom ran away or hid for fear of being taken into an Ebola Treatment Center. There were logistical difficulties in finding contacts, particularly in rural areas where some tracers were known to hike hours in very difficult terrain to find contacts. Some contacts were hostile, angry and flat out denied that they had interactions with a sick person. Many refused to give their names or to comply with self-enforced quarantine. Contact tracing in densely populated slums and urban centers was challenging. It was nearly impossible to determine how many contacts one patient had in a community where everything is shared, including mattresses, toilets, living quarters, and caring for children and for the sick (195).

'Off the grid' cases and incomplete contact tracing is thought to be the reason why the outbreak was initially thought to have burned out in April and May, 2014 only to reemerge more vigorously in the early summer (3). Clusters of undocumented cases were brewing in rural areas, out of the reach of epidemiologic surveillance. It is believed that

infection in these hidden areas reached critical mass until, eventually and inevitably, an infected patient from these unknown clusters had contact with someone in the community or with someone who would make his or her way into an urban center. Once the virus reemerged in May, it proved impossible to stop.

6. Safe and Proper Burial Since the beginning of the outbreak, removal and proper burial of the dead has been a source of controversy. West Africans hold funeral rite sacred and had a difficult time abandoning them despite the fact that traditional burial practices pose a great risk of viral transmission. Tradition dictates that after death bodies are kept in the home for several days or weeks, during which time they are washed and prepared for burial. The post mortem viral titers in the bodily fluids and blood of a deceased Ebola patient remain high and provide an opportunity for the virus to be transmitted to those who care for the body. During the wake, it is customary for mourners to touch and kiss the deceased before they are buried posing a risk of transmission to all of the mourners. Some often travel great distances to attend and when they return home, they take the virus with them (226; 228; 230).

The actual transport of bodies themselves back to home cities or districts for traditional burial ceremonies also opens up another avenue for transmission. Families are known to frequently transport dead bodies themselves without proper protection in order to organize funerals in other towns, opening up avenues of transmission to those who provide the transportation and help move the bodies (227). The most publicized occurrence was the case of the Imam in Mali in November who died in Mali but was

transported back to Guinea for his funeral, from which over 300 contacts were identified (232).

Because of the high risk of transmission associated with customary funeral practices, in August, Liberian president Ellen Johnson Sirleaf decreed that all bodies of Ebola victims in Monrovia be cremated in an effort to curtail funeral transmission (229). However, this ruling has unintended consequences: shortly after it was made more than half of the beds at Ebola Treatment Centers were found empty, despite the fact that this was a time of intense transmission and high incidence of Ebola cases. Instead of obeying the mandate, families were electing to care Ebola patients at home instead of seeking treatment at Ebola Treatment Centers, which amplified the cycle of transmission (228). Burials in Liberia are not allowed without a death certificate confirming a non-Ebola death, therefore when the sick eventually died, family members went so far as to bribe Ebola response teams for death certificate or to turn a blind eye as they carried out traditional funeral and burial rites in secret (230). It is also possible that these bribes were offered so families could avoid the stigma of having to admit a family member died of Ebola.

Outside of Monrovia, the rest of Liberia was not required to cremate the bodies of Ebola victims, but they were obliged to ensure that bodies were buried safely to eliminate the possibility of transmission. Guidelines issued by the Center for Disease Control called for the bodies to be handled only by those trained in the removal of infected human remains; to be wrapped in plastic shrouds; and buried in hermetically sealed caskets (231; 228). However, many of these bodies were interred in mass unmarked graves, even though this was in violation of the safe and dignified burial standard operating procedure.

Family members should have been allowed the opportunity to observe the burial of a loved one, but were denied that right. As a result, families still hid and cared for Ebola patients at home and buried them in secret according to their tradition (228; 229).

Conclusion

As Ebola transmission begins to decline in West Africa, it is necessary to look to the future and put systems in place that will prepare the region in the investigation and control of emerging infections. The Human Development and Multidimensional Poverty Indices of all three countries in West Africa indicate that people are living in conditions that are extraordinarily deprived. The majority of the population is poor, malnourished, and live without proper sanitation, all circumstances that leave them susceptible to disease, both endemic and epidemic. Corrective measures and new systems should include lessons learned from the current Ebola outbreak.

The health care infrastructure in Liberia, Guinea and Sierra Leone remains weak and inadequate. After decades of civil unrest, the region was only beginning to reestablish health systems and to see marginal improvements in some reported health indicators, but these populations remain vulnerable to other health crises. Incident tuberculosis has been rising gradually since 1990 in Sierra Leone and Liberia, and these patients will most likely not receive routine care or medicines. While the reported maternal and infant mortality rates have declined since 1990, whether they are underreported or not, they are still among the highest in the world. After Ebola left health systems decimated, many pregnant women don't have a professional to see if they experience complications (248). Childhood immunization rates have been steadily increasing, but they are still much lower than in the developed world, and fall short of the percentage necessary for herd immunity. In particular there is concern that lapses over the past year in measles vaccination campaigns have left the country susceptible to a measles outbreak, which could cause death rates on par with the Ebola epidemic itself (247).

In addition to concerns about routine health measures, Ebola has illuminated the necessity for rebuilding infrastructures and constructing emergency systems that can be activated in the event of another health emergency. While the proportion of GDP that has been spent on health care infrastructures in Liberia and Sierra Leone has increased over the past decade (Guinea continues to spend the least of the three countries, dedicating less than 10% of GDP to health care infrastructures), any gains that were made have been destroyed over the past year. Basic systems need to be rebuilt, such as opening more hospitals and equipping them with basic infection control supplies, such as medications, gloves, disinfectants, and masks: materials that were reported to be unavailable when Ebola struck.

There also needs to be an active surveillance system put into place that is staffed with well-trained professionals who can be sent to the field when an outbreak occurs. Epidemiologists and medical teams need to be ready to be dispatched to identify cases. Primary health care facilities and laboratories must be built for better diagnoses and clinical management. Once cases are identified and reported, contact tracers need to be activated immediately to find potential cases. While such a system will require significant financial outlays, the infrastructure, once in place, will be a useful, life-saving investment. There are endemic diseases in West Africa, such as Lassa fever, yellow fever, meningitis, malaria, and cholera that can be contained by such a system. A measles vaccination campaign could also be expedited by the structure that this system could provide.

The swift action that contained the virus in Nigeria as well as in the Firestone Plantation in Liberia are prime examples of how Ebola in an urban setting does not have

to end with a high case fatality rate. Nigeria had the polio eradication program infrastructure in place to facilitate Ebola control measures, which expedited the Ebola surveillance and containment process. At the Firestone Plantation, as soon as the first case arrived in late March/early April 2014, the company activated the existing organizational framework and redirected resources to contain the outbreak using standard measures such as active and passive surveillance, case identification, and proper infection control procedures. The same type of infrastructure can be built and maintained in West Africa, but financial resources must be directed to the area.

Human capital is equally as imperative. Before the outbreak, there was a dearth of doctors and nurses and those who remained often went on strike over salary issues and other demands (those strikes and demands continued throughout the outbreak amongst doctors, nurses, contact tracers, and ambulance drivers, and burial teams). Ebola has decreased the number of health care providers even further. As of March 25, 2015, there have been 853 health care workers who were diagnosed with Ebola and 494 of them have died.

It is necessary to replenish the health care cadre in West Africa by exploring other training approaches. For example, the method of doctor training and education that exists in Cuba might serve as model to follow. In 1998, the Cuban government established the Latin American Medical School, which gives scholarships to low income students around the world and provides them with an education (249). The understanding of the program is that upon completion of their training, doctors will return to their home countries to practice medicine. As of 2014, more than 23,000 physicians have graduated from the program. With seed money from the global health community, this type of scholarship

program for West African medical students could provide the region with the doctor pool it needs to help support a newly rebuilt health care infrastructure. It would incentivize education and bring much needed medical personnel to the area.

Ebola, and indeed many other outbreaks, are fought and overcome on the village level, but this latest outbreak has shown that disease can spread exponentially, and outbreaks seemingly never end, without trust in public health messages and adherence to containment protocols. Good communication and community engagement are vital to "combat denial, rumors, and behaviors that can fan new transmission chains" (194). To that end, community and religious leaders are a necessary component of the surveillance and communication. It is imperative to bring all local and grass roots leaders into the fold and encourage their participation in surveillance and delivering containment messages. This fosters trust in the community and can help emergency response systems work more efficiently.

Ebola outbreaks in the past have heretofore been elusive and abbreviated, leaving researchers with very little scientific evidence they can use to study the virus. The 2014 outbreak has provided a large number of cases and survivors to allow the scientific community the opportunity to examine the risk factors for death and short and long-term outcomes. There is now more information about the potential positive effects on patients who receive oral rehydration therapy. While the effect of the treatment has not been studied in a randomized and controlled environment, enough anecdotal evidence has been gathered that educated hypotheses can be formed. This may be helpful in the clinical management of future Ebola outbreaks and could save lives.

Vaccine and other clinical trials have been rapidly rolled out over the past year and well-powered studies are now possible given the case loads in West Africa. While the development of the drug Brincidofovir has been abandoned by Chimerix and the Faviporavir trials revealed that more research on the drugs effectiveness is needed, there are currently trials underway that are studying the effectiveness of ZMapp, blood/plasma therapy, and TKM-Ebola.

The development of a safe and effective vaccine could give health care workers and other front line responders the protection they need to keep themselves safe and to administer more comprehensive care in the early days of an epidemic. Early results from the chimp adenovirus vector vaccine showed safety and immunogenicity, and Phase II and Phase III clinical trials are being run at the time of this writing in West Africa.

Only time and more studies will tell if an effective therapy or vaccine can be developed. The concern going forward is that after the last of the Ebola patients have been buried or return home, the scientific community will move on to something else, Ebola therapeutics will be deprioritized, and all gains will be abandoned. As populations continue to grow and more and more people move to urban areas seeking economic opportunity (5), the likelihood of Ebola resurfacing in a densely populated city is likely. The outbreak of 2014 has shown us that Ebola, or indeed any other 'rare' disease, can quickly spread, take thousands of lives, destroy communities, and become a global threat.

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