Faculty of Health Sciences

The 2013-2016 West African Ebola Epidemic

An overview of central aspects

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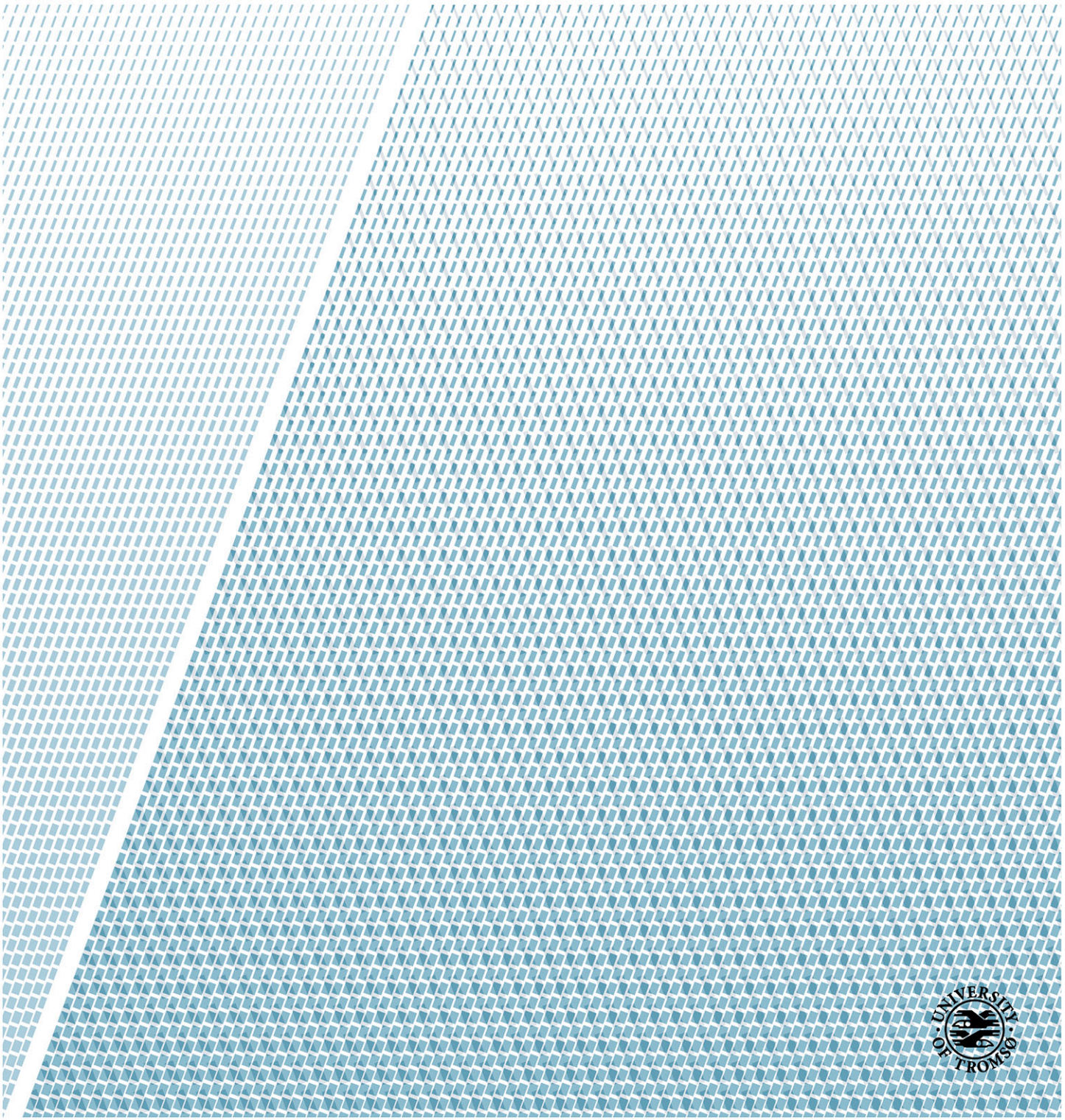

Preface

When we were assigned to write a thesis the autumn of 2016, I was on an exchange program in Pretoria, South Africa. I have always had an interest in infectious diseases and epidemiology and wanted this to be the topic of my thesis. The university published a list of available projects and one of them entailed the 2013-2016 West African Ebola epidemic. I thought this would be an interesting topic for a thesis due to its unique circumstances. I contacted Ørjan Olsvik who was listed as the supervisor. We agreed that a suitable purpose would be to provide an overview of some of the central aspects regarding The Epidemic.

I wish to express my gratitude to my supervisor, Professor Ørjan Olsvik for helping me illustrate some of the important and challenging factors for the unprecedented scale of the 2013-2016 Ebola epidemic. Furthermore I wish to thank him for his commitment, engagement and for all the fascinating discussions during this process.

The process of constructing and writing a thesis has been challenging at times, but also instructive and rewarding. I want to express my appreciation to my family and friends for their support.

This report is conducted without any financial support.

Olga Bellos

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Table of contents

Abstract

Background

Ebola is a filovirus and one of the most virulent organisms identified. It's a zoonosis with fruit bats as the likeliest reservoir. Pathogen spill-over from infected animals causes human outbreaks with subsequent human-human transmission. The purpose of this thesis is to provide an overview of central aspects of the 2013-2016 West African Ebola Epidemic.

Methods

This thesis is based on references retrieved through the search engine PubMed, online WHO and CDC documents and on personal communication. References were sorted according to inclusion and exclusion criteria: language, abstract and full-text availability. Search results were scanned and screened by title and further assessed for relevancy by reading the abstract. External references were included after screening reference lists of included articles.

Results

Ebola was in 2013 a novel agent in West Africa. It took 3 months before its probability was identified. The rural epicentre with 80% forest loss is in proximity to borders of Liberia and Sierra Leone. Case amplification occurred through burial ceremonies and health facilities. The populations are highly mobile and convenient access across borders and to cities existed. A total of 815 probable and confirmed cases of health worker infections were identified from 01.01.14-31.03.15. CFR was 2/3. Most health worker infections occurred outside Ebola Treatment Units (ETUs). Several risk factors in the work setting were identified and opportunities for community-acquired infections also existed. The keys to stop transmission include rapid detection of cases, construction of ETUs, contact tracing, safe burials and strict adherence to established protocols. The rVSV-ZEBOV vaccine show promising results.

Conclusion

West Africa's lack of experience with Ebola, delayed identification, geographical and demographic characteristics contributed to the scale of The Epidemic. A high number of infected health workers were observed with many potential risk factors, both in and outside work settings. This undermined the overall response to The Epidemic. Preventative measures aim to break subsequent chains of transmission. These were challenging during The Epidemic, contributing to the scale.

List of Abbreviations

CDC	Centers for Disease Control and Prevention
CFR	Case fatality rate
EBOV	Ebola virus
ELISA	Enzyme-linked immunosorbent assay
DC	Dendritic cells
DIC	Disseminated intravascular coagulation
DRC	Democratic Republic of the Congo
ETU	Ebola treatment unit
EVD	Ebola virus disease
GP	Glycoprotein
HW	Health worker
IFN	Interferon(s)
IL	Interleukin
IPC	Infection prevention and control
KGH	Kenema Government Hospital
MSF	Médicins Sans Frontières, Doctors without borders
NO	Nitric oxide
NP	Nucleoprotein
PPE	Personal protective equiptment
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
TNF	Tumor necrosis factor
TF	Tissue factor
VHF	Viral haemorrhagic fever(s)
VP	Virion protein
WHO	World health organisation

1. Introduction

1.1 Viral haemorrhagic fevers (VHF)

VHF is a syndrome caused by several different RNA-viruses (1) with some common features: humans are not the natural reservoir for these viruses primarily due to high mortality rates. A virus is dependent on a living organism in order to replicate its genome. The host of VHF viruses is an animal or insect and when in direct contact with humans or non-human primates the virus may be transmitted. Human-human transmission occurs from an infected individual to another (2). Human outbreaks are also difficult to predict since they occur only sporadically. Geographical distribution is *usually* restricted to the areas inhabited by these species (3).

Table 1 provides an overview of the five different families of viruses known to cause VHF in humans with their animal host, example of virus and example of VHF (4).

Family	Animal host	Example of virus	Example of VHF
Arenaviridae	Rodents	Lassa virus	Lassa fever
Bunyaviridae	Arthropods and rodent	> 300 different, e.g. Nairo virus	Crimean-Congo haemorrhagic fever
Paramyxovirida	Fruit bats	Mumps, measles and Hendra virus	Hendra virus disease
Flaviviridae	Arthropods	Yellow fever virus, dengue virus	Yellow fever, dengue fever
Filoviridae	Fruit bats	Marburg and Ebola virus	Ebola Virus Disease

Table 1. Overview of the 5 families that are known to cause VHF, their animal hosts, with example of virus and the disease they cause (4).

A common pathophysiological feature is damage to the vascular system that facilitates capillary leakage. Furthermore VHF impairs the body's ability to regulate basic functions, such as blood pressure (5). Clinically VHF poses a diagnostic challenge because symptoms vary from mild to life threatening. The severity differs from the one disease to another, but also between patients (5). Generally, a patient with VHF has an abrupt onset of fever, myalgia and headache followed by vomiting and diarrhoea**.** Thereafter signs of haemorrhage may develop (although this is rarely fatal). End-stage disease involves DIC and hypotensive shock (2, 5, 6)

Although outbreaks usually are restricted to local rural areas with large impacts on local communities, VHF also constitutes an international challenge through import of these infections and also as their potential as weapons in biological warfare (6)

The Ebola virus is an archetype of the viral haemorrhagic viruses because it demonstrates all the points made above. The virus is one of the most virulent organisms known and has an ability to cause profound disease in mankind with case-fatality rates up to 90%. Therefore it's also classified as a biothreat pathogen category A(7)

1.2 Purpose

An outbreak of Ebola in late 2013 became an epidemic, with the most substantial impact caused by this virus the world has ever seen. This epidemic will therefore also be the focus of this thesis. The overall objective is to provide an overview of different aspects of the epidemic. It will attempt to provide certain explanations that contributed to the unprecedented scale. A review all problems that occurred would be impossible due its magnitude and complexity. On that note there are some research questions that needs to be answered:

1. What distinguishes this outbreak from the previous epidemics, with a specific focus on its origin, spread, demographic and ecological contributors. This will include an overview of previous epidemics.
2. One particularly serious feature in this epidemic was the substantial number of infected health care workers. How were the features and contributing factors?
3. What are some of the key elements to stop an Ebola outbreak and how are they conducted?

1.3 Taxonomy

In order to understand fundamental pathophysiology, treatment options and vaccine development it's essential to possess some fundamental knowledge of how the Ebola virus is structured.

1.3.1 Classification + the story about how Ebola got its name.

Yambuku is a small village northern Democratic republic of the Congo and is the place where Ebola was discovered in 1976. The discovery was followed by a discussion about what name

to give the virus. Dr. Peter Piot, one of the co-discoverers of Ebola discusses this in his book "No time to lose (8)." When the Lassa virus was discovered in 1969 it was named after the place of discovery. This was also an option now, but the research team decided on another option because they did not wish for the village to become a symbol of catastrophe (as had happened with the Lassa virus). Therefore, it was suggested to name the virus after the closest river. Apparently the Ebola river was the nearest to Yambuku. In local language Ebola means "black river". In the end it turned out that the map that had been used was inaccurate. The Ebola river wasn't the closest river, but the name had already been given and has persisted ever since(8)

Ebola is a member of the Filoviridae family, with three viruses being classified in this family: namely the Ebola virus, Cuevavirus and Marburg virus. The name filoviridae has its origin from the Latin word filum, meaning "thread-like" (9). Under an electron microscope filoviriradae have a thread-like appearance.
There are 5 known species of the Ebola virus, namely Zaire, Sudan, Tai Forest, Bundubugyo and Reston(10). The first 4 will cause profound disease in humans(11)

1.3.2 Structure and genetics

Ebola is an enveloped, non-segmented single stranded negative sense RNA virus (12). The capsid coats the genetic material (RNA) and is formed by individual protein molecules called capsomeres. The nucleic acid together with the capsid is called nucleocapsid.
The Ebola virus has also an outer lipid membrane derived from the host cell, this is called the envelope. The envelope has attached viral glycoproteins.

The shape may vary from long filaments to shorter filaments formed like a "6" or "U", a biological feature known as pleomorphism. The strands measure from about 80 nanometres up to 14 000 nm. The RNA genome has a helical shape and 19000 nucleotides form the genome with seven structural proteins as end products(9). They are in following order: 3' leader, nucleoprotein (NP), virion protein 35 (VP), VP 40, glycoprotein (GP)/soluble GP, VP 30, VP 24, RNA-dependent RNA-polymerase, 5' trailer (9, 13).

The ribonucleoprotein complex is formed by the RNA genome and is encapsulated by nucleoprotein that forms the capsid. VP35, VP30 and RNA-polymerase associate with the genome and capsid to form the nucleocapsid structures.

Viral VP 40 and 24 are matrix proteins responsible for structural integrity. VP 40 is involved in viral budding. VP 24 has an important role in IFN-supression. The only surface protein is Glycoprotein (GP). Glycoproteins are proteins with carbohydrate groups attached to their chain. In the Ebola virus GP has a trimeric appearance. An enzyme called protein convertase furin (from the host) makes different subunits of glycoprotein. GP1 facilitates attachment to the host cells, whereas GP2 is responsible for fusion of the membranes. A third GP, known as soluble GP is secreted in large amount from infected cells (9, 14). Table 2 provides with a summary of the viral proteins and their functions.

Viral protein	Function
Nucleoprotein	Forms the capsid of the virus
VP 35	Non-structural protein. IFN antagonist
VP 40	Matrix protein between capsid and envelope. Involved in viral budding (particle formation)
GP	Surface protein. GP1: attachement GP2: fusion of membranes
VP 30	Non-structural protein
VP 24	Matrix protein between capsid and envelope. Suppresses IFN-production
RNA-polymerase L	RNA-polymerase

Table 2: A summary of the different viral proteins and their functions.

1.4 Life cycle

1.4.1 Entry of the host cell

Viruses are distinct from living organisms because they are dependent on a host in order to replicate. The first step in this process is therefore the entrance into the host cell. The exact entry mechanism for the Ebola virus into the host cell is only partially understood. As mentioned earlier GP facilitates anchoring and entry, but exact how is unknown (9, 13).

However, viruses similar to the Ebola virus enter their host cell through endocytosis, this is a process where viral particles are engulfed and released into the cytoplasm of the cell. Different modes of endocytosis have been identified and different viruses depend on different routes (9, 13).

Clathrin-mediated endocytosis is a well understood endoctic mechanism. Invagination of the plasma membrane occurs in specific areas of the cell membrane called clathrin coated pits. Another route of endocytosis is Caveolin-mediated endocytosis and takes place in parts of the plasma membrane rich in cholesterol (lipid rafts) and caveolin protein with a flask shaped invagination of the plasma membrane. Disturbance in cell membrane cholesterol reduces the viruses abilities to enter the cell (13) . Earlier studies have suggested that the Zaire strain of Ebola virus uses the clathrin route (15) or the caveolin route (16). This has been disproven in a later study conducted by dr. Saeed and his team (13). The same study showed results that indicate that Zaire Ebola virus most likely enters the cell through micropinoctyosis in HEK293T and Vero cells. This is supported by the fact that inhibiton of proregulators of macropinocytosis limits viral entry and infection. Dr. Saaed points out that its unknown if the viruses uses macropincotyosis in other cells, but argues that this is an endocytic mechanism that most cells possess. Furthermore this study proved that after cell entry virus trafficking was facilitated through endosomes, but where the release of the nucleic acid occurs is still uncertain (13).

1.4.2 Ebola virus transcription

With the Ebola virus being a negative sense RNA-virus, conversion to a positive strand of viral RNA is necessary before translation. RNA polymerase aids the conversion to the positive strand within the cell. Thereafter translation of mRNA is facilitated and viral proteins are produced.

1.5 Ebola virus disease (EVD)

1.5.1 Viral reservoirs

The widest accepted theory is that fruit bats serve as a natural host for the Ebola virus. An appropriate natural reservoir is able to live with the infection and not die from it. If the natural reservoir dies from the viral infection, the virus would die out. In other words: if Ebola was to be fatal in bats they could not serve as a reservoir and the virus is therefore persistent in the

bats. Infected bats can transmit the virus to other animals such as apes, but also to humans. Human infection usually occurs after contact with infected (that are either sick or dead) animals like gorillas, chimpanzees, porcupines that are found in the forest(17, 18). After an infected individual develops symptoms of EVD human-human transmission may occur. Figure 1 illustrates how Ebola virus ecology and transmission takes place.

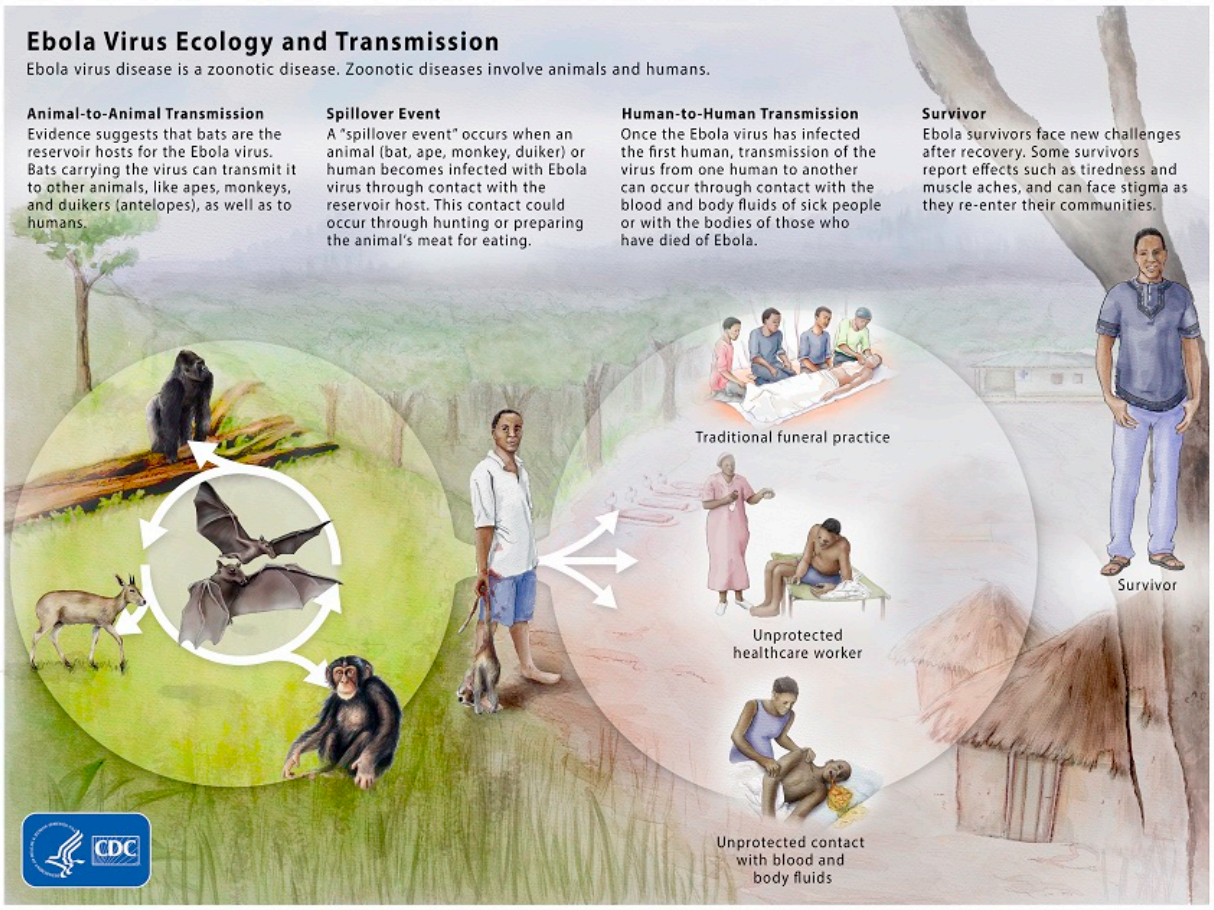


Figure 1. An overview of Ebola Ecology and transmission (11)

1.5.2 Modes of transmission

Two factors determine the likelihood of human-human transmission:

1. The type of infectious medium
2. The viral load in that medium.

When secretions infected with Ebola come in direct contact with a broken skin barrier and/or mucous membranes human-human transmission arises. Blood, faeces and vomit are examples of infectious secretions that are also the most infectious. The virus may also be found in breast milk, saliva, semen and tears. Indirect transmission occurs through contaminated surfaces and objects, e.g. linens (19). Traditional burial rituals where the mourners are direct

contact with the deceased have contributed to the extensive transmission seen in the local communities(17). As an example 85 confirmed Ebola cases were linked to one funeral ceremony in Guinea (20).

Ebola as a sexual transmitting disease

Studies have shown that the Ebola virus can persist in male semen up to 9 months after onset of symptoms. This has started a discussion about the virus' ability to be transmitted sexually. However this exact mode of transmission is still uncertain (21).

1.5.3 Pathophysiology

After viral entry into the human body, macrophages and dendritic cells are probably the first cells to be infected. When Ebola replicates in these cells it causes apoptosis and thereby the release of new viral particles in the extracellular fluid occur. Table 2 illustrates that at least two viral proteins have the ability to interfere with IFN I responses: VP 35 is and IFN antagonist and VP 24 supresses IFN production. This facilitates rapid systemic spread (22). Replication in regional lymph nodes results in dissemination to liver, spleen, thymus and other lymphoid tissues. Multifocal necrosis in liver and spleen is a fatal stage of this process (23).

As a response to infection the infected cells of the body produce systemic inflammatory cytokines and other proinflammatory mediators. Infected macrophages produce TNF-a, IL-1b, IL-6 as well as NO (nitric oxide). This cascade causes substantial damage. It is thought to be one of the leading causes of gastrointestinal (GI) dysfunction and is known to cause capillary leakage. Another theory for GI dysfunction is viral infection of the GI tracts. Capillary leakage lays a foundation for a process known as extravasation meaning that the leucocytes migrate out of the blood vessels towards the site of infection. However in EVD soluble glycoproteins released form virus infected cells prohibit extravasation and therefore also interfere with the immune system's ability for viral attack (24). Furthermore the leukocytes that are stuck in the vessels release proinflammatory cytokines leading to further damage to the blood vessels and also stimulations of the coagulation cascade. The leakage from the capillaries to the interstitial space is harmful because it leads to loss of blood volume and development of hypotension and in worst-case scenario hypotensive shock.

Another important pathophysiological feature is Ebola's ability to cause coagulation defects. Infected macrophages synthesize tissue factor (TF) leading to activation of the extrinsic coagulation pathway. Additionally, the proinflammatory cytokines trigger the macrophages to produce TF. This leads to the development of coagulopathy, a coagulopathy of consumption since the stimulation of the coagulation pathway leads to thrombosis and the consumption of the coagulation factors leads to bleeding. At later stages hepatic failure may also lead to declined production of certain coagulation factors.

A central event when battling infections is the enablement of the adaptive immunity and subsequent antibody production. In EVD, this process in impaired. The dendritic cells (DC) are one of the primary cells in which Ebola replicates. They are also the cells responsible for antigen presentation to naive B-lymphocytes and therefore essential in the initiation of adaptive immune responses. Studies have shown that the dendritic cells are unable to mature and therefore also incapable to serve as antigen presenting cells in people dying from Ebola. Simultaneously, survivors have early and increasing levels of IgG directed against NP and VP40 (25, 26). A deadly EVD infection also leads to apoptosis of lymphocytes leading to further impairment of adaptive immunity. This phenomenon is possibly induced by the inflammatory mediators and/loss of stimulation from the DC (23, 27).

1.5.4 Symptoms and clinical findings

Figure 2 illustrates how EVD progresses in humans. After an incubation period of 2-21 days an infected patient will start to develop fever, headache, fatigue and myalgia (28). Subsequent symptoms are vomiting, watery diarrhoea, chest pain, coughing with declining liver and renal functions. 5-7 days after onset of symptoms, signs of haemorrhage *may* develop. Common manifestations include bloody stools, petechiae, ecchymoses, mucosal bleedings and oozing from venepuncture sites. Simultaneously with the haemorrhagic symptoms a diffuse erythematous, nonpruritic maculopapular rash may arise. Predilection areas include the face, neck, truncus and arms. A progressive stage of the disease includes shock and DIC (14, 17, 28-30). An end stage illness is characterised by the development of meningoencephalitis with altered mental status, disorientation and seizures(31)

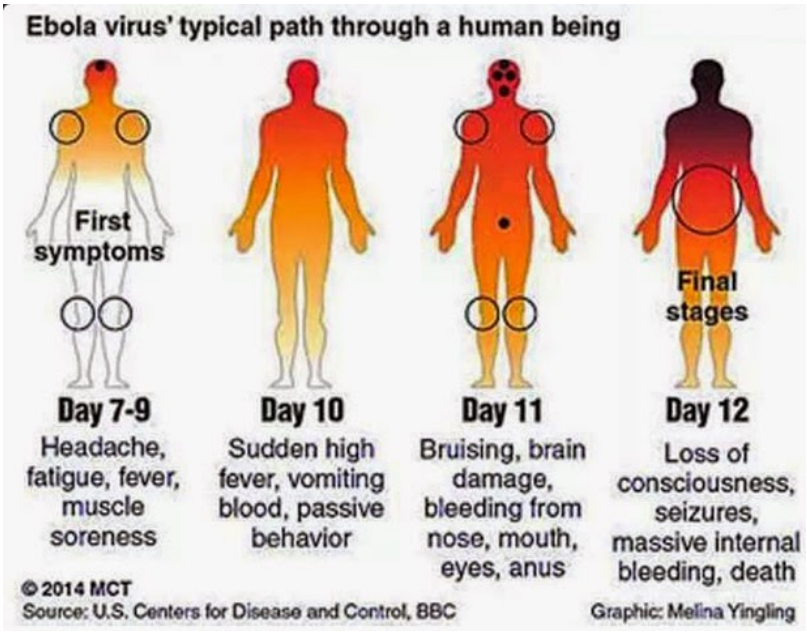


Figure 2: A Demonstration of the clinical course of EVD in humans (32)

Especially two clinical features were distinguishable compared to symptoms in previous epidemics:

1. Traditionally, severe haemorrhage was one of the dreaded and serious complications, thus naming the disease "Ebola haemorrhagic fever." However, during the latest epidemic fatal haemorrhage was less prominent. Consequently the name changed to "Ebola virus disease."

2. Vomiting and diarrhoea was recognised as two symptoms that contributed to more severe illness than previously acknowledged. This was due to large volume losses and electrolyte disturbances(33).

1.5.5 Diagnosis and laboratory findings

The initial symptoms of EVD are non-specific and resemble many other illnesses more common, e.g. Malaria. However it's a diagnosis one should always keep in mind especially in people with connection to Central and West Africa. Viral detection may be done the by following investigations:

- Reverse transcriptase polymerase chain reaction (RT-PCR)
- Antibody-capture enzyme linked immunosorbent assay (ELISA)
- Electron microscopy
- Virus isolation by cell culture (17)

A typical biochemical picture in a patient with EVD is leukopenia, thrombocytopenia and transaminase elevations. Electrolyte abnormalities like hyponatremia, hypokalemia/hyperkalemia, hypomagnesemia and hypokalsemia are common. At later stages coagulation abnormalities consistent with DIC are manifest (17, 30).

1.5.6 Disease course and recovery

In Ebola survivors, clinically improvement is typically seen during the second week of illness. Patients with fatal illness tend to present with more severe signs and symptoms in the early stage of the disease. Progression to multi-organ failure and death occurs on a general basis when the survivors tend to improve, i.e. during the second week of illness. The recovery time after surviving EVD is long lasting and may continue for more than two years. Common complaints include fatigue, headache and problems with regaining weight. Acute arthralgia, retro-orbital pain, uveitis, hearing loss and different skin conditions are not uncommon. Some symptoms may be more serious than others. Different postulations have been made on reasons for these symptoms. Some have suggested that a higher viral load in early stage of disease may be the reason, some reports suggest that immune activation plays an important role (33).

2. Materials and Methods

This thesis provides an overview of different events that occurred during the 2013-2016 West African Epidemic that contributed to it scale. It is based on relevant literature retrieved from PubMed, WHO and CDC documents retrieved at their respective websites as well as information given to me by my supervisor Ørjan Olsvik.

2.1 Definitions (34)

Incidence: the rate of occurrence of a disease stated as the number of new cases of the disease in a given population in a given time.

Prevalence: Presence/occurrence, i.e. the fraction of a given population that has a given disease at a certain point.

Endemic: A communicable disease that over a longer time period is restricted to a certain geographic area or population.

Epidemic: WHO has defined an epidemic as the following: "The occurrence in a community or region of cases of an illness, specific health-related behaviour, or other health-related events clearly in excess of normal expectancy. The community or region and the period in which the cases occur are specified precisely. The number of cases indicating the presence of an epidemic varies according to the agent, size and type of population exposed, previous experience or lack of exposure to the disease, and time and place of occur." (35)

Pandemic: An epidemic so widely spread that vast numbers of people in different countries and even continents are affected. WHO has defined a six-phased pandemic classification system. It is mainly used to describe influenza pandemics, but it is applicable for other epidemics too. The six phases are:

- Phase 1: No animal (influenza) virus circulating among animals has been reported to cause infection in humans
- Phase 2: An animal (influenza) virus circulating in domesticated or wild animals is known to have caused infection in humans and is therefore considered a specific potential pandemic threat.
- Phase 3: An animal or human-animal (influenza reassortant) virus has caused sporadic cases or small clusters of disease in people, but has not resulted in human-human transmission sufficient to sustain community level outbreaks

- Phase 4: Human- to- human transmission of an (animal or human-animal- influenza reassortant) virus able to sustain community- level outbreaks has been verified.
- Phase 5: The same identified virus has caused sustained community level outbreaks in two or more countries in one WHO region.
- Phase 6: In addition to the criteria in phase 5, the same virus has caused sustained community level outbreaks in at least one other country in another WHO region (36).

Outbreak: More cases than expected of a given disease restricted to a geographic area in a limited timeframe or ≥ 2 cases of the same disease with presumed common source of infection

Lethality: An expression for the seriousness of a given disease, i.e. the fraction of those with a given disease that die as a result of the disease.

Mortality: Death rate, the number of deaths in a defined population during a given time.

Reproduction rate (R_0): Is a measure to calculate how many people a person with a communicable disease will transmit the disease to during his/hers time of illness in a totally susceptible population (no immunity). In other words: the number of secondary cases per case. If $R_0 < 1$ the illness will burn out, $R_0 > 1$ the disease will continue to spread and if $R_0 = 1$ the disease will stay endemic (37).

Health worker: All those who work in health services, including drivers, cleaners, burial teams and community based workers and clinical staff (38).

2.2 WHO classification of EVD cases

Classification	Criteria
Suspected	Any person, alive or dead who has (or had) sudden onset of high fever and had contact with a suspected, probable or confirmed Ebola case, or a dead or sick animal OR any person with sudden onset of high fever and at least three of the following symptoms: headache, vomiting, anorexia/loss of appetite, diarrhoea, lethargy, stomach pain, aching muscles or joints, difficulty swallowing, breathing difficulties, or hiccup; or any person with unexplained bleeding OR any sudden, unexplained death
Probable	Any suspected case evaluated by a clinician OR any person who died from "suspected" Ebola and had an epidemiological link to a confirmed case but was not tested and did not have laboratory confirmation of the disease
Confirmed	A probable or suspected case is classified as confirmed when a sample from that person tests positive for Ebola virus in the laboratory.

Table 1. WHO definition of EVD cases (38).

2.3 Search strategy, selection criteria for the literature

The aim was to find literature on the problems mentioned in the introduction. Publications on these problems were therefore also the inclusion criteria for this thesis. Since there were several problems I wanted to review I found it appropriate to preform separate searches for each problem that is to be highlighted. All relevant literature had to cover the West African Ebola epidemic of 2014-2016. A combination of literature obtained from the search engine PubMed, WHO publications and published CDC documents were the foundation for this thesis. The search for literature was conducted from March 2018-end of April 2018. Although separate searches for literature for each problem was preformed, some common features can be identified:

1. For each problem separate literature search in PubMed was preformed as well as retrieving relevant WHO and CDC documents from their respective websites. Relevant articles may also have been included after screening reference lists of other articles.
2. In order to narrow down the number of articles some inclusion and exclusion criteria were made:
    a. Documents must regard the 2014-2016 epidemic only, except when retrieving information regarding previous epidemics
    b. Studies written in other languages than English were excluded
    c. Documents not available in free full text through University of Tromsø's online access or retrieved from my supervisor was also excluded
3. After the literature searches were completed, the search results were scanned and screened by reading the title.
4. Articles with relevant title were further screened for relevancy by reading the abstract.
5. The articles were added to the digital reference handling medium EndNote X8.

2.3.1 Epidemiological features

A search was conducting in the search engine PubMed in the beginning of April 2018. A combination of the following search terms was used: "Ebola virus disease" "Africa" "West Africa ""epidemiology" "epidemiological features" and "2014". Filters used were "abstract," "free full text" and time period 01.01.14-01.01.18. Four additional articles were included after screening reference lists. In Addition CDC has published an overview of previous epidemics that is the foundation for that part of this text. WHO published a one-year report where

several important factors are discussed and included in this report. In total 8 articles are included in addition to the CDC publication.

2.3.2 Ebola in Health Workers

The intention was to find relevant literature on the amount of infected health workers and the reasons for this. A search in PubMed with the following combinations was made: Ebola in health personnel, Ebola virus disease in health personnel, Ebola in health worker, Ebola virus disease in health workers. PubMed allows you put on filters in order to customize the search:

1. Text availability: Here I chose to put on the filter for abstract and free full text, as this was a requirement for this paper.
2. Publication dates: was in this thesis limited to 01.01.2014-31.12.2017.

The search terms were all added to the builder in PubMed with the word "OR" in between. This resulted in 22 articles. 5 articles found to be relevant after screening the titles and abstracts. One article was excluded after reading the whole article due to irrelevancy. In addition one WHO publication on this subject was included as well as two articles after studying the reference list of the included articles. In total, 7 articles were included.

2.3.3 Infection control

The aim was to identify some important strategies to prevent/reduce transmission of EVD. This is a complex process and it would be impossible to discuss all aspects in this thesis. However, after discussion with my supervisor we decided on some strategies that would be suitable to discuss (these will be presented later). One previously used source was found to be suitable again. Furthermore, both WHO and CDC have published many documents and guidelines on the chosen topics. All these publications are fully available at their online website. One article published in Lancet was accessed through the WHO website.
Some points are also based on personal communication between my supervisor Ørjan Olsvik and myself. In total, 8 references were included in this part.

3. Results

3.1 Epidemiological features of the 2014-2016 West African Epidemic

3.1.1 Previous outbreaks

Table 3 provides an overview of all epidemics up until 2013 (39). Ebola was first identified in 1976 by two temporal related, but separate outbreaks. One was caused by the Zaire strain of Ebola virus (EBOV) and occurred in the town of Yambuku in The democratic Republic of the Congo (DRC). 318 cases with 218 deaths were identified (Case fatality rate, CFR 88%). The other was caused by the Sudan strain and affected 284 people of whom 151 died (CFR 53%). Up until 2013 there have been 21 identified outbreaks in addition to the two first. Zaire and Sudan Ebola virus have been the causative strains in the majority of outbreaks, with 12 and 7 outbreaks respectively (39).

The countries that previously have experienced EBOV outbreaks are located in central Africa. DRC, South Sudan, Congo, Gabon and Uganda have had multiple outbreaks. A two case outbreak occurred in South Africa in 1996. The Ivory Coast has had 1 case that occurred in a zoologist that had preformed an autopsy on a chimpanzee. Studies showed that the strain was of Tai forest type (39-41).

Prior to 2013, outbreaks have been of lesser size with only 7 cases affecting > 100 people. The largest epidemic before 2013 was in Uganda in year 2000. The causative agent was Sudan Ebola virus with 425 identified cases. However, with 224 deaths lethality (53%) was significantly lower than previous epidemics (39).

In an article Shears and O'Dempsey classify the previous outbreaks in three groups: 1. Outbreaks occurring in remote forest areas, linked directly to bush meat consumption and usually with few cases. 2. Those centred around and within regional hospitals with considerable hospital transmission, spreading into the community. 3. Those occurring in populated rural areas, with mainly hospital transmission but some transmission in local health facilities (42). What all the previous outbreaks have in common is that they have been time-limited and restricted to one country.

Country	Town	Cases	Deaths	Species	Year
DRC	Yambuku	318	280	Zaire	1976
South Sudan	Nzara	284	151	Sudan	1976
DRC	Tandala	1	1	Zaire	1977
South Sudan	Nzara	34	22	Sudan	1979
Gabon	Mekouka	52	31	Zaire	1994
Ivory Coast	Tai Forest	1	0	Taï Forest	1994
DRC	Kikwit	315	250	Zaire	1995
Gabon	Mayibout	37	21	Zaire	1996
Gabon	Booue	60	45	Zaire	1996
South Africa	Johannesburg	2	1	Zaire	1996
Uganda	Gulu	425	224	Sudan	2000
Gabon	Libreville	65	53	Zaire	2001
Republic of Congo	Not Specified	57	43	Zaire	2001
Republic of Congo	Mbomo	143	128	Zaire	2002
Republic of Congo	Mbomo	35	29	Zaire	2003
South Sudan	Yambio	17	7	Sudan	2004
DRC	Luebo	264	187	Zaire	2007
Uganda	Bundibugyo	149	37	Bundibugyo	2007
DRC	Luebo	32	15	Zaire	2008
Uganda	Luwero District	1	1	Sudan	2011
Uganda	Kibaale district	11*	4*	Sudan	2012
DRC	Isiro Health Zone	36*	13*	Bundibugyo	2012
Uganda	Luweo District	6*	3*	Sudan	2012
Multiple	Multiple	28652	11325	Zaire	2014-2016

*Numbers reflect laboratory confirmed cases only

Table 1: An overview of all known epidemics up to 2014 (39)

3.1.2 2013-2016 West African epidemic: Geographic origin and spread

In a one-year report by WHO it was described that *"A mysterious disease began silently spreading in a small village in Guinea on December 26th 2013"*(43). In March 2014 WHO was notified of this disease where patients presented with fever, severe diarrhoea, vomiting and high fatality rate. Baize et al. conducted a virologic investigation and identified Zaire EBOV as the causative agent for this mysterious disease (40). Figure 1 is a timeline that demonstrates major events during the West African outbreak (41).

An epidemiological investigation was conducted and the index case was identified as a 2-year old boy in Meliandou in Guéckédou prefecture (40, 43). This is a small, rural village in a forested region of Guinea(43). The initial investigation conducted by Baize et al. indicated that the boy fell ill in the beginning of December 2013 and died a few days later. The following investigation revealed that the death of the index case was dated to the end of December 2013 (40). The exact source of infection remains uncertain (43), but a tree infested with fruit bats was the boy's play ground (44).

In the beginning of January 2014 close family members (sister, mother, grandmother) of the index case developed similar symptoms and died rapidly. These symptoms were also observed in midwives, traditional healers and hospital staff in Guéckédou who treated them. In the week after, extended family members of the index case who attended funerals or who cared for sick relatives became ill and died (43). By February 1st 2014 the virus had reached Guinea's capital, Conakry by an infected extended family member of the index case's family. Adequate precaution measures weren't implemented, as EVD wasn't a diagnosis anyone had experienced in this region. By the end of February cases spread to other regions, villages and cities in Guinea (43).

During March 2014 the disease had spread further in Guinea and the first reports of cases in Liberia occurred (40, 43, 45). The first cases occurred in the Lofa County, close to the Guinean border. By April 7th 2014 Liberia had 21 confirmed, probable and suspected cases with 10 deaths (43). In their one-year report WHO refer to a retrospective study that traced down the first case in Sierra Leone to a woman that had been a guest at the home of the index case in Meliandou, Guinea. She travelled back home to Sierra Leone when the host family became ill and she died in the beginning of January 2014. No report or investigation followed this death (43). From the end of May-beginning of June 2014 an exponential growth of cases was noted in Sierra Leone. These cases were traced back to a traditional healer in a village in Kailahun district close to the Guinean border. Guinean Ebola patients crossed the border to be treated by this healer and transmission occurred.

The burial of the healer was followed by a domino effect of more cases, deaths and funerals. Consequently, 365 cases were traced back to that single funeral. Freetown, the capital of Sierra Leone experienced the first confirmed case on June 23rd (43). Figure 2 below is a map

of all the districts in the three countries that were most affected by Ebola (45). By July 2014 case counts were increasing, and The Epidemic had reached several towns and the three capitals of Guinea, Liberia and Sierra Leone, namely Conakry, Monrovia and Freetown (45).

On August 8th 2014 WHO declared the epidemic to be a *"public health emergency of international concern"*(45). The Epidemic spread further to other African countries and also to Europe and The United States. In total, 36 cases of Ebola were reported from Italy, Mali, Nigeria, Senegal, Spain, the United Kingdom and the United States (41, 44). From late autumn 2014 case counts started to decline, but cases were still identified throughout 2015. The Epidemic was declared to be over in March 2016 with 28 652 cases, 11 325 deaths and 17 300 survivors (44).

Figure 1. General timeline documenting key events during the 2013-2016 West African Ebola Epidemic (41)

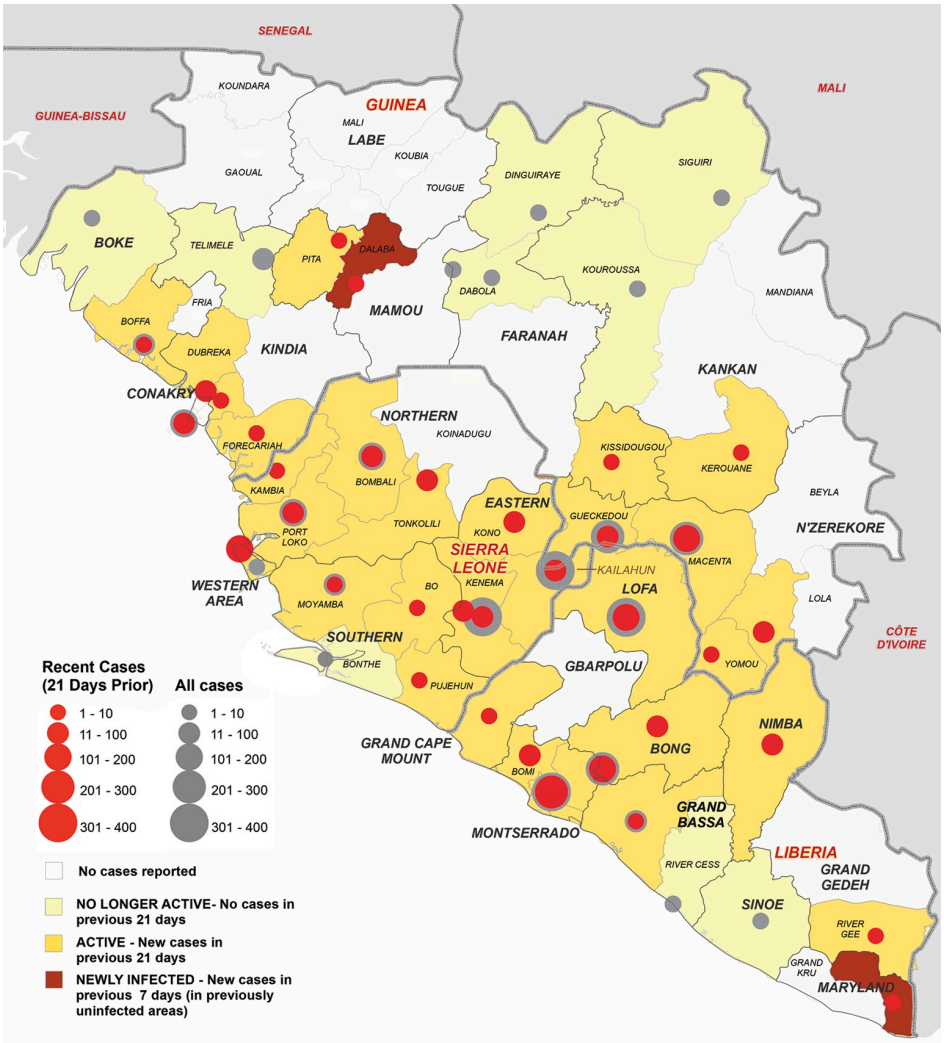


Figure 2. Districts affected by EVD in Three countries in Africa. The map shows the districts that have been affected by EVD in Guinea, Liberia and Sierra Leone. Grey circles indicate the total numbers of confirmed an probable cases reported in each affected district, and red circles the number reported during the 21 days leading up to September 14th, 2014 (45)

3.1.2 Distinguishing features of the 2013-2016 West African Ebola Epidemic

From the events described above, one can identify several features that differentiate the 2013-2016 West African Ebola Epidemic from the previous epidemics up until 2013.

The 2013-2016 Epidemic outranked all previous outbreaks in cases, survivors, deaths and duration. It was 67 times the size of the Uganda outbreak of 2000, which was the largest outbreak up until 2013 (44). Previous epidemics were mainly located in central Africa and mostly in rural areas. Many of these countries have experienced several outbreaks (table 1). The 2013-2016 Epidemic was mainly localised to three countries in West Africa but other African countries like Nigeria and Senegal also reported cases of Ebola. For the first time a trans-continental spread by air travel to Europe and the United States took place and thus involving developed nations. None of these countries had experienced Ebola before. The epicentre for the outbreak was localised to the countryside a massive spread to more

populated areas and major cities including all three capitals of the three most affected countries was seen (41, 43-45).

3.1.3 Viral origin and contributing factors from an ecological, environmental and demographic perspective

When the virus materialised in West Africa, the question about its origin was raised. In the study conducted by Baize et al. a phylogenetic analysis of the gene sequence of the EBOV strain was preformed. It revealed that the strain causative for the 2013-2016 Epidemic was similar and closely related to other EBOV strains, but not identical to those responsible for outbreaks in The Democratic republic of the Congo (DRC) and Gabon. These findings indicate that the virus has evolved in parallel with the strains from DRC and Gabon from a common ancestor instead of being introduced into Guinea. Fruit bats are common in large parts of West Africa (40).

The epicentre for the 2013-2016 West African Ebola Epidemic was in the Forest Region of Guinea. The region has experienced a forest loss > 80% due to foreign mining and timber operations. This has brought the bats in closer contact with the humans. Before symptom debut the index case was playing close to a tree infested with bats (43). Forest loss as a contributing factor for human exposure to bats is posed as a source of infection in the available literature (43, 46, 47)

The populations in Guinea, Liberia and Sierra Leone are highly mobile both within their countries and across the three national borders. Population mobility in this area is 7 times higher than other countries in the world (43). Boarders between the West African countries could be crossed easily and there were convenient connections between villages, rural towns and national capitals (41, 43, 45-47). Furthermore, for the first time the introduction of Ebola to different population occurred through air travel, for instance in both Lagos Nigeria and Dallas Texas.

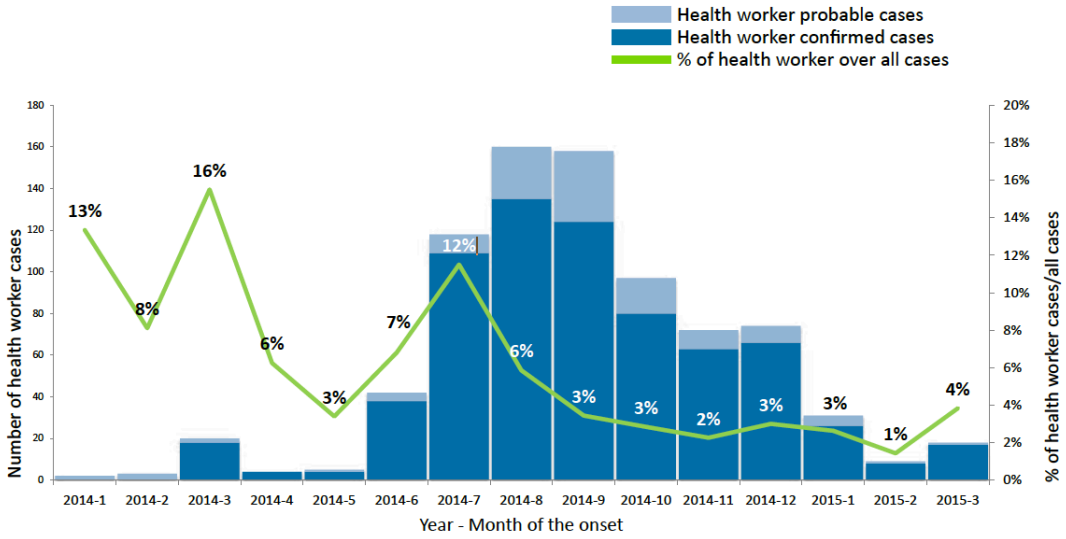
Another contributing factor that has been pointed out in the literature is West Africa's lack of experience with Ebola. Hospital staff had never treated EVD cases before, the laboratories had never analysed patient samples. Ebola as causative agent wasn't on the radar when patients with mysterious symptoms first were reported (43). Many other diseases that are

endemic to this region can present with similar symptoms as EVD. Lassa fever, a Viral Haemorrhagic fever (VHF) endemic to the region and was a more likely diagnosis (41, 43). Cholera is also prevalent in West Africa, and in early stages EVD and Cholera resemble each other. A one-year outbreak of Cholera was seen in Guinea and Sierra Leone in 2012. Cholera was therefore not an unlikely diagnosis. Microscopic examinations of patient samples examined by a team including staff from Mediciniers Sans Frontiers (MSF) revealed bacteria and the hypothesis of Cholera as causative agent was strengthened. This was in late January-beginning February 2014. No final conclusion was drawn at that time and further investigations were conducted. Ebola virus, Zaire species as causative agent was identified in late March 2014. An outbreak was announced on WHO website March 23rd 2014. By that time 49 cases and 29 deaths were officially reported (43).

3.2 Infected health workers

3.2.1 Epidemiology and demographics

A WHO report revealed that from January 1st 2014 to March 31st 2015, 815 probable and confirmed health worker EVD cases were recorded in VHF database. Sierra Leona, Liberia and Guinea were the three countries where The Epidemic had the most substantial impact with 328, 288 and 199 cases of EVD in health worker in each country respectively. 225 additional suspected cases were reported, but not included in the WHO report. In this time frame health workers accounted for 3.9% of all confirmed and probable cases reported. As a proportion of all monthly number of cases, health worker infections peaked in July 2014 at 12% and declined to a low of 1% in February 2015 (38).



*All cases include health worker and non-health worker confirmed and probable cases.

Figure 3. Number of confirmed and probable health worker EVD cases over time (and proportion of health worker cases among cases reported) in Guinea, Liberia and Sierra Leone combined, January 1st 2014 – March 31st 2015 (38).*

Of the infected health workers, 61% were males. The males represented 95% of the medical workers (table 6, annex 1 (38)), 88% of the laboratory workers, 77% of the trade and elementary workers and 45% of the nurse workers that were infected. In the report the health workforce databases have been researched revealing that males were disproportionally affected with the male: female ratio being 1.6:1. Based on occupation, nurses, nurse assistants and nurse aides accounted for > 50% of all health worker infections. Medical workers accounted for 12%, whereas laboratory workers 7%, elementary workers (janitors, maintenance staff etc.) 7%(38). In Guinea doctors were significantly more affected by EVD compared to Sierra Leone and Liberia (38, 48). Depending on the health profession, the risk of EVD infection was between 21-32 times higher in health workers compared with non-health workers ≥ 15 years of age (38).

When comparing health workers to non-health workers 77% of health workers where hospitalized compared to 62% of non-health worker ≥ 15 years old ($p<0.01$) (38). When comparing the time from symptom onset to isolation in these two groups, a report from Guinea didn't show any discrepancy (48).

A total of 6 out of 7 included articles report that most of the infected health workers worked in other facilities than dedicated Ebola Treatment Units (ETU's) (48-52). This is illustrated by a Morbidity and Mortality weekly report published by the CDC: From June 9th –August 14th 2014 97 cases of Ebola were identified among health workers in Liberia, 62 (64%) of these

cases were part of 10 clusters of health workers working in non-ETU facilities. Seven of the ten clusters were associated with hospitals, one cluster included health workers in two clinics and a hospital and one patient visited all three locations during time of illness. The last two clusters were health workers working in two separate clinics. A total of 50 out of the 62 cases had confirmed Ebola with 31 identified deaths. Table 2 summarises the details. In this report one additional cluster was identified in health workers working in a dedicated Ebola facility (ETU) (49). The Kenema district in Sierra Leone experienced one of the biggest clusters of EVD cases in health workers that have been reported. From May 2014-January 2015 600 EVD cases were uncovered, 92 were health worker infections. A majority of the health workers (66 cases) worked at Kenema Government Hospital, a hospital that prior to the outbreak served as national referral centre for Lassa fever with a dedicated ward that was turned into an ETU. In total, 18 of the 66 infected health workers worked in the ETU, whereas the 48 remaining persons held positions elsewhere in the hospital (52). Investigations preformed on a cluster of health workers working in en ETU and an adjacent hospital (Hospital A) in Liberia revealed EVD infection in 5 health workers. Three of the infected health workers worked in both the ETU and hospital A, the remaining two worked in the Emergency department of Hospital A (53).

Characteristic	Number
Total number of cases	62
Confirmed cases (deaths)	50 (31)
Health care workers per cluster	2-22 (median =5)
Clusters in health facilities that were not Ebola treatment units	10
Hospitals with a cluster of Ebola among health care workers	8
Clinics with a cluster of Ebola among health care workers	4

Table 2: Characteristics of identified clusters of Ebola virus disease among health care workers in health care facilities that were not Ebola treatment units- Liberia, June 9th-August 14th, 2014 (49)

For health workers with final outcome available, CFR was calculated in the WHO report. With 635 end results available and 418 death CFR was 2/3. This number was lower than for the rest of the population (non-health workers), but CFR showed also a variation between countries. In Guinea CFR amongst health workers was significantly lower than in Sierra Leona and Liberia. Guinea was also the country with the most complete data for that variable

(38). CFR was somewhat higher in females than in males, 68% to 65%, but the variable was not statistically significant (p=0.5)(38).

Olu et al conducted a retrospective descriptive study on health workers in Sierra Leone from May-December 2014. Almost half of the infected health workers believed that exposure had occurred in a hospital setting, 19% assumed exposure had taken place at home, 17.8% believed that exposure had occurred at health centres and 5.1% from other health facilities. Among those believing exposure had occurred at home, 41% reported physical contact with a family member, 20% reported contact with another health worker and 9% reported contact with a friend. In total 91% of the infected health workers reported contact with an EVD patient within the 21 days before symptom onset (51). The WHO report points out that transmission not unlikely occurred in the communities, outside hospital settings with or without providing care for EVD patients (38). A report from investigations conducted on health workers in Sierra Leone revealed that a significant number of health workers and non-health workers had participated in funerals or been in contact with a corpse, but health workers were less likely to have attended funerals than non-health workers. Health workers were more likely to have been in contact with an Ebola patient 30 days prior to symptom onset than non-health workers (50). Data from investigations on health workers working in other facilities than ETU's revealed that 60% of the Ebola cases occurred in health workers working at hospitals, but other treatment facilities also experienced health workers being infected with Ebola. In two of the described health worker-clusters health worker-EVD-patients had prior to symptom onset provided care for infected patients in home settings (49). Another study conducted on health workers in Kenema, Sierra Leone described that 13% of the health workers contacts prior to their onset of symptoms were other patients and 27% were other infected colleagues. Some sporadic reports on health workers providing care for EVD patients at home without sufficient PPE were also described in the article (52).

3.2.2 Possible risk factors and determinants for health worker infections in work settings

Several determinants and risk factors that have contributed to health worker infections have been established. Most of them focus on problems that occurred at the work place. A summary is available in table 2. Several breaches in protocol were reported, some of the most common problems were: lack of/inadequate triage systems, insufficient Infection prevention

and control (IPC) training, no general IPC policies; including inadequate supervision and lack of equipment. Other problems that occurred commonly were infrastructural problems regarding physical space and layout (38, 49-53).

Possible determinant	Details
Administrative shortcomings	Lack of or inappropriate point of care risk assessment • Cadaver exposure • Standard and transmission based (from blood and bodily fluid exposure) precautions not universally followed • No reassessment of admitted patients to identify new symptoms of Ebola • Delayed lab diagnosis of Ebola cases
	Problems with patient flows and zoning • Inadequate triage of Ebola patients and deceased patients • Inadequate control of Ebola patient or health worker movement within health facilities
	Lack of IPC staff and policies • Lack of standard operating procedures and clearly assigned responsibilities for IPC • Lack of IPC specialists
	Lack of supplies and training • Lack of/inadequate equipment, materials, training, monitoring of PPE use and decontamination • Limited capacity or inadequate training on safe management of contaminated waste • Limited capacity or inadequate training on the safe management and burial of the deceased
Engineering and environmental controls	Inadequate isolation and barriers • Inappropriate or inadequate isolation areas/setup • Lack of delineation between high-risk and low-risk Ebola zones • Inappropriate, inadequate or absent barrier nursing • Infrastructure limitations with lack of barriers separating general wards from Ebola patients • Limited availability of safe transport vehicles for patients and the deceased
	Lack of environmental controls • Poor hygiene and contaminated equipment and surfaces • Lack of or insufficient hand hygiene stations, soap, running water, alcohol-based hand rubs, chlorine/bleach/cleaning supplies, electricity, working waste disposal system
PPE problems	Insufficient/inadequate PPE and inappropriate use of it • Inconsistent use of PPE • Multiple use of disposable PPE • Health workers in hospital refusing to wear PPE while taking care of a relative
Defective practices/exposure at the point of care	• Inadequacies or inconsistencies in hand hygiene practises • Inadequacies or inconsistencies in biological specimen sampling • Needle stick injuries • Touching mucous membranes while wearing PPE (e.g. rubbing eyes with contaminated glove) • Smoking while wearing PPE • Usage of mobile phone while wearing PPE

	• Health worker providing care at home • Health worker embracing an ill colleague
Employment conditions, social and environmental factors	• Delayed and unpredictable remuneration • Staff shortages • Exhaustion (long working hours) • Psychosocial stress • Lack of social protection for illness

Table 3. Possible determinants and risk factors of health worker infection during the 2013-2016 West-African Ebola Epidemic. The table is adapted from WHO with contribution from other reports (38, 49-53)

3.3 Containment measures

In the 9-month WHO report mentioned earlier the basic reproduction numbers were calculated to 1.71 for Guinea, 1.83 for Liberia and 2.02 for Sierra Leone. The total number of cases were estimated to pass 20 000 cases in total by the beginning of November 2014 if further strategies to prevent transmission weren't implemented (45).

In order to reduce/stop the transmission of EVD many tools are necessary, some features are summarised in figure 4. According to Ørjan Olsvik the keys to stop an outbreak are early/rapid detection of cases with subsequent admission to an ETU and safe burials. He also points out that sufficient hygiene and strict adherence to rules are essential (54). Another tool to prevent further person-person transmission is contact tracing (55). The 2013-2016 Epidemic highlighted the need for research and as an example the results from a large vaccine clinical trial will be presented.

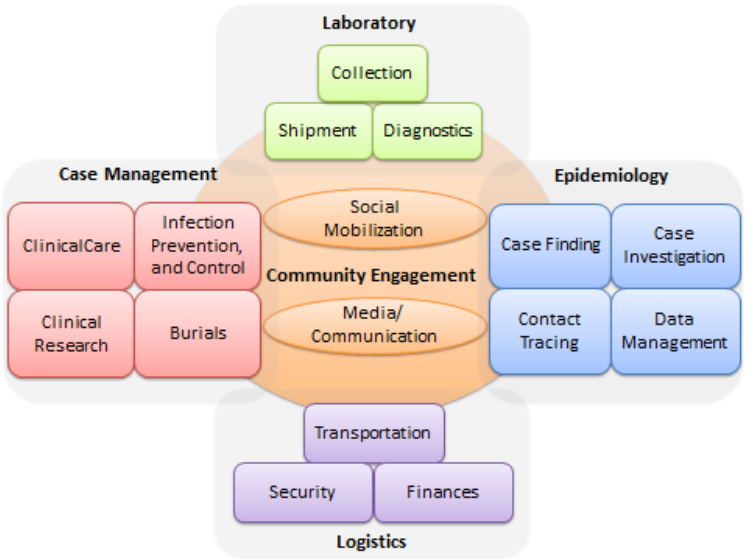


Figure 4: Structure of the different committees involved in EVD outbreak control activities (55)

3.3.1 Structure of the ETU

A triage area is located outside the ETU with a purpose to identify EVD patients(56). Patients with classical symptoms of EVD including bleeding from nose and mouth were isolated immediately (54). Surrounded by a fence, two zones constitute the ETU itself: the low-risk and high-risk zone. A double fence separates the high-risk zone from the low-risk zone. The low risk area is a staff area and contains changing area, storage, pharmacy etc. The high-risk area is divided into two areas: a suspected and a confirmed area. Only patients and health workers wearing PPE are allowed to enter the high-risk area. In the suspected area patients are tested for EVD. If the lab test is positive, the patient will be moved to the confirmed area. Is the test negative the patient is discharged and leaves through a special exit after disinfection. The flow in the ETU is designed for patients and staff to always move from low-risk to high-risk area or from suspected to confirmed area. Once a patient enters the confirmed area there are two ways to leave it: through the confirmed area in the same fashion as in the suspected area or through the morgue. The morgue is always within the confirmed area with a safe exit. There is also a staff-designated exit in the high-risk area (56).

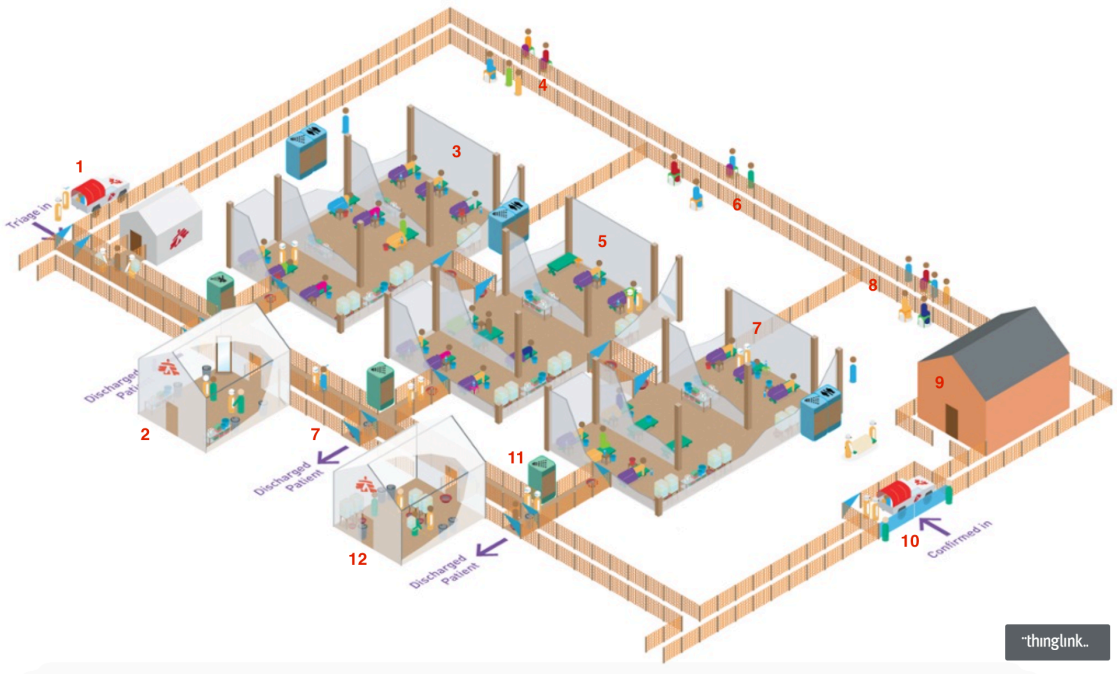


Figure 5. Structure of an MSF ETU (57). 1: triage area, 2: Staff dressing room, 3: Ward for patients with low probability of Ebola, 4, 6, 8: Visitors area, 5: Ward for patients with high probability of Ebola, 7: Ward for patients with confirmed Ebola, 9: Morgue, 10: Entrance for patients with already identified Ebola, 11: Decontamination shower, 12: Undressing room for staff. Note that there is a slight between in the high- risk zones between the CDC explanation and MSF

3.3.2 Burials

WHO has developed guidelines on how to conduct burials that are safe, but at the same time are respectful towards the deceased and those left behind. It's emphasised that only trained personnel should conduct the burials. The 12-step guideline describes the steps from prior to departure to the burial itself. The team typically consists of 8 people including members wearing full PPE, 1 sprayer, a communicator and a religious representative. The guidelines stress that informed consent always must be obtained before the burial can be conducted. Religious views should be respected to possible extent, and separate guidelines for Muslim and Christian patients are developed. The technical execution entails the wearing of PPE before contact with the remains, placement of the corpse in a body bag, environmental sanitation, transportation of the body bag to the cemetery and placement of the body into the grave. The community should also be involved in prayers at the burial site (58).

3.3.3 Contact tracing

WHO has defined contact tracing as *"the process of identifying, assessing and managing people who have been exposed to a disease to prevent onward transmission (55)."* Figure 5 illustrates the relationship between Case Management and Contact tracing with basic principles for conduction. Infrastructure (alert system, ETU, laboratory etc.), personnel, resources and funding enable contact tracing. An Investigation Team conduct systematic interviews of potential EVD cases in order to reveal all possible contacts since symptom debut. The interview is conducted with the aim to identify all people who possibly have been exposed to transmission through the symptomatic patient. That includes
People in which the case has had physical contact with, share household, visitors, places the contact has visited (included health care facilities and health workers in contact with the case). If the case is a health worker all patients must be listed. Relatives/next of kin should always be interviewed. A detailed procedure with specific instructions on how to conduct contact tracing is available in the WHO guidelines (55). Identified contacts are then asked about EVD symptoms and then monitored for 21 days since the last contact with the case (55).

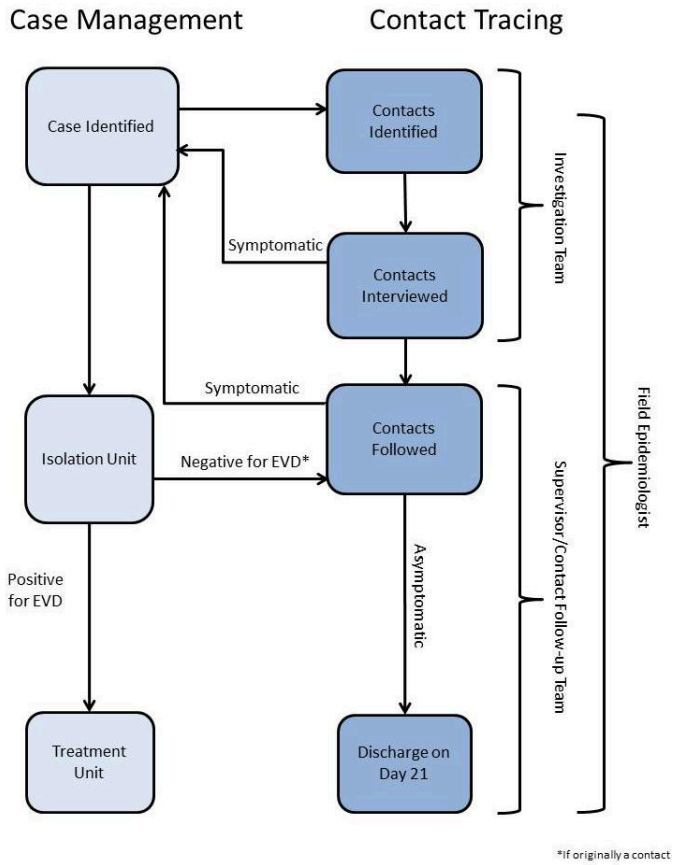


Figure 5: Relationship between Case Management and Contact Tracing in the EVD Response (55).

3.3.4 Vaccination

During the 2013-2016 West African Ebola Epidemic research on possible vaccine candidates was conducted. A dozen different candidates underwent clinical development/trial, but only the rVSV-ZEBOV vaccine completed stage III during the epidemic (59).
On December 23rd 2016 WHO published a press release stating that rVSV-ZEBOV vaccine provides high protection against the disease (60).

The results of this open-label, cluster-randomised trial conducted in Guinea and Sierra Leone were published in The Lancet. Contacts and contacts of contacts of a confirmed EVD case were defined as a cluster (ring). The clusters were then randomised to immediate vaccination or postponed vaccination at 21 days with 51 and 47 clusters, respectively. The pre-specified primary outcome was a laboratory confirmed case of EVD at 10 days or more from randomisation. The study then compared how many cases of Ebola that occurred in the immediate vs. the postponed vaccination group. An independent monitoring board recommended that the randomization should be stopped since immediate vaccination showed promising results. Consequently, immediate vaccination was offered to all identified rings, and children 6-17 years. No cases of EVD occurred 10 days or more after randomisation in

those assigned to immediate vaccination vs. 16 cases in the delayed cluster. This constituted a vaccine efficacy of 100% (61).

4. Discussion

4.1 The Epidemiological aspects

Bats are stated as the likeliest animal reservoir of the Ebola virus. In these species the virus is persistent, but does not cause clinical disease. On occasion pathogen spill-over into a human population is observed. The host response in humans is different from that in bats and causes EVD, a severe sometimes-fatal illness. It has the potential to cause substantial human-human transmission.

Table 2 provides an overview of all the past outbreaks, the number of cases and deaths plus the Ebola species responsible. As seen, the Zaire Ebola virus has been responsible for several outbreaks with high case-fatality rates. The Sudan virus has also caused a number of epidemics, but the Case Fatality Rate (CFR) has been somewhat lower than for Zaire. The Tai Forest virus has only been identified in one individual who survived. The Bundibugyo virus was first recognized in an outbreak Uganda in 2007 with a CFR significantly lower than for Zaire and Sudan virus, around 30%. Reston virus has only been found in an animal reservoir in the Philippines. It was identified in 1989 when it caused an outbreak and deadly infection in macaques imported into the United States. It caused several outbreaks amongst non-human primates in imported animals from the Philippines to US and Europe. This strain isn't known to cause severe symptoms in humans and it is shown that IgG antibodies against the virus can be produced (23). This demonstrates that Ebola isn't just Ebola, there are several different species with varying pathogenicity and deadly potential. These differences and possible viral changes should be monitored for future purposes because killing its host is self-defeating since viruses are dependent on their hosts' replication machinery to survive.

Several of the Central African countries have had previous experience with Ebola outbreaks. This favours rapid containment of epidemics in several ways: even though the symptoms are diffuse, the health workers have a reason to suspect EVD. The illness is understood, the response measures and laboratory capacity is established several places (43). This way cases are detected at an early stage, isolated and further transmission may be prevented. Even though the health systems and infrastructure are weak in these countries, having experience with a disease and how to handle it is important, as WHO point out (43). On that account, this can partly explain the unique extent of the 2013-2016 West African Epidemic. The medical personnel did not think of the possibility that Ebola was the causative agent. In order to make

a diagnosis you have to think of the possibility of it. That the focus was on other highly prevalent diseases like malaria, cholera and Lassa fever is yet understandable. This may have contributed to confusion because of similar clinical symptoms in early stage. Yet, it took 3 months before it was realised that Zaire Ebola virus was the causative agent, thus giving the virus time to spread throughout the populations. At this time, the outbreak was already at a comparable size with several of the previous epidemics (table 2). Furthermore, all necessary infrastructural containment measures were lacking in these areas (43). Early and correct identification of the causative agent will be instrumental for future epidemics. As an example, during the current (May 2018) outbreak of Ebola it took 4 days from the first cases were reported to the causative agent was identified by RT-PCR on May 7th (62). Finally, as fruit bats are common in large parts of West Africa (40), EVD should always be considered as a differential diagnosis.

Although the index case of The Epidemic was traced back to a two-year-old boy in the small village Meliandou, some uncertainty remains on when the boy became sick. The findings in this report indicate that the boy became ill in the beginning of December 2013, but a follow up investigation dated symptom debut and death to late December. This is also in accordance with WHO details (43).

The available literature could not establish exactly how the boy contracted Ebola. What Baize and colleagues conclude is that the virus has existed in West Africa for a significant amount of time due to the genetic differences to Zaire viruses responsible for previous epidemics (40). The findings further indicate that a tree infested with bats was in the boy's backyard/playground. This could provide opportunity from transmission, supported by a report by Saéz and colleagues. However, the authors point out that other children also played in this tree thus providing a massive opportunity for transmission (63). Furthermore, other hypotheses on possible sources were explored. Exposure to infected mammals was excluded as a possibility since these populations were stable in size. Another theory was linked to the handling of bush meat. This was also considered unlikely for a number of reasons: no hunters were reported as family members, if infected bush meat was brought by a hunter outside the family, that hunter would probably also be among the first infected. Handling of infected bush meat would affect the adults at the same time as the 2-year-old (63). Therefore, exposure to bats through the infested tree is the likeliest source of infection, even though it cannot be 100% proven.

Another challenge is to establish the exact consequences of forest loss in this region as the reason for pathogen spill-over. At this point the exact role may be difficult to identify, but closer and more frequent encounters between humans and bats could provide opportunity for human transmission and not only through the handling of bush meat. Given the bats presence in this region, and how common it is to handle bush meat, human EVD epidemics are rare. One would maybe expect epidemics to have occurred more frequently and earlier in this region. Consequently, challenges in explaining the timing of the spill-over event remain. For now, bats are identified as the likeliest reservoir, but if other sources also exist, this remains unknown. This uncertainty and the possible ecological factors contributing to human exposure highlights the need for further research. Hopefully future findings would provide important insight to easier predict future outbreaks. Up until such time, the whole West African region should be considered at risk, thus underscoring the importance of future preparedness (40).

The human-human transmission from the index case to family members demonstrates some of the factors contributing to amplification of cases and some of their issues. First, close family members were the first to contract the disease. This is not that surprising as transmission often is difficult to limit within a household where most facilities, including bathrooms and cutlery are shared. Additionally, with the index case being a toddler one would expect that he received care from close family and thus providing severe opportunity for transmission. In fact it is very common in West Africa to provide care for sick family members in home settings. As the Norwegian psychologist Ane Bjøru Fjeldsæter wrote in her book "De Uberørbare" (Eng.:"The Untouchables") about her field experience in West Africa: "caregiving is Ebola's secret weapon."(64).

Furthermore, introduction of the disease to health care settings generated more cases. Amplification of cases from the index case also occurred through funerals and the 2013-2016 epidemic led to a substantial increase in numbers. Illustrated by the fact that 360 cases were traced back to the funeral of a traditional healer. Another example of this is demonstrated by findings documented in a mortality and morbidity weekly report (MMWR) from the Moyamba district in Sierra Leone. A burial of a pharmacist generated 28 new confirmed cases, and that in a district that had a low incidence of EVD. 21 of the subsequent cases had reported touching the man's body at the funeral, 16 had direct contact with him prior to his death (65).

In previous epidemics geography aided containment. Most of them occurred in rural areas far away from populated cities. Limited distribution favours rapid containment in such settings, as control measures are easier to implement and only a few coordinating facilities are needed. In West Africa the geographic characteristics facilitated the magnitude of The Epidemic. Figure 2 demonstrates that the epicentre for the outbreak is in proximity of both Liberia's and Sierra Leone's border. It wasn't just the geographic proximity in itself hat caused the magnitude. It has to be seen in the light of the highly mobile populations, as the findings reveal. When extremely convenient cross border traffic is added to the equation, rapid dissemination of the disease can be explained. Some explanations for the high population mobility in these countries are described in the literature: Poverty is an important driver as it forces people to travel in order to find work and food. In addition, in West Africa it is common to have relatives in other countries and mobility is therefore enhanced (43).

The geographic and demographic characteristics complicated control measurements. For instance, contact tracers did not cross the national borders (43), with the consequences being suboptimal contact tracing and that unidentified patients spread the disease. Section 4.3 highlights the importance of a robust response system. When one country experiences declines in case count, new clusters were introduced from neighbouring countries seeking more available treatment facilities (43). This highlights the importance of cooperation between all countries and also one coordinating organ for all countries. Under those circumstances no country was safe until eradication was a fact in the whole region.

Convenient connections did not only exist *between* the three countries. Movements from the rural areas to more populated areas, including all three capitals facilitated the spread and made the magnitude possible. In many of the West African cities large parts of the populations are poor and live densely in townships. This is often exacerbated by inadequate hygiene conditions, thus providing severe opportunity for transmission. Furthermore, implementation of control measures can be demanding in such settings. Just imagine the challenges with conducting contact tracing in multi-million cities. Despite of this, control can be achieved as seen in Nigeria with the introduction of Ebola to Lagos. This had the potential to become a catastrophe, but the outbreak was limited. First, the country was prepared for cases, as they had been witness to widespread transmission in their neighbouring countries for months. Furthermore, in the years prior to the outbreak a Polio Operations Centre served as a coordinating unit to battle Polio. This structure was successfully adapted in the EVD response

ensuring a unified coordinating unit (43). Close collaboration with the governmental Ebola Emergency Operations Centre (EEOC) and global organisations like Centers for disease control and prevention (CDC), World Health Orgainzation (WHO) and Médicins Sans Frontières (MSF) was instrumental (66). The conduction of contact tracing in Nigeria is also a story of success. GPS systems were implemented and contacts were instructed to stay at home and at least avoid crowded areas, for 5 contacts group quarantine was utilized due to high-risk exposure (67). All contacts were followed up daily (43). At the end of the Nigerian outbreak almost all contacts were accounted for and sufficiently followed up (43, 68). According to Ørjan Olsvik Nigeria and Mali are the only countries were a thorough epidemiological investigation and contact tracing were conducted (69).

Another aspect of the introduction of Ebola virus (EBOV) to capital cities with international airports was the transcontinental spread with the following fear for a pandemic. Gomes and colleagues conducted a study on the assessment of the international spread risk in 2014 and the findings state that the risk was small, but not insignificant. The authors stressed that the risk would increase if control measures weren't improved, and especially if the Nigerian outbreak escalated (70). However, to state that international spread was limited due to the Nigerian containment would be wild speculation. Therefore, all countries should have the facilities to isolate and treat EVD patients and have protocols on containment of spread even though the risk is small.

The temporal characteristics of this epidemic permitted for increased genomic variation of the EBOV according to Professor Martin Hibberd at London School of Hygiene and Tropical Medicine (71). A study conducted by Gire and colleagues revealed a very high viral mutation rate during the 2013-2016 West African Ebola Epidemic with frequent non-synonymous mutation (which alter the amino acid sequences and are therefore subject to natural selection). Hebberd discuss that the increased genomic variation can have different effects on the clinical picture of EVD in humans. One possibility is increased viral load that leads to increased transmission to others and/or a more severe course of disease. Another possibility is that alteration of the genome sequences lead to a lower viral load, but the time of infectiousness is longer, thus permitting transmission to more people (71). A second study conducted by Dietzel and colleagues on the functional significance of three non-synonymous mutations was investigated. They studied the significance of three different mutations: 1. In the gene for L polymerase, one receptor part of the GP and finally a part of the NP. The results indicate that

the mutations impact on the different viral proteins. A recombinant EBOV with all the three mutations showed growth advantage compared to a prototype lacking the named mutations in cell cultures (72). However, the studies could not determine what exact role this played for transmissibility and pathogenicity the West African Epidemic, although they stressed that progression of The Epidemic could lead to viral adaption (72, 73). Furthermore Hibberd points out that the selection process takes a long time and in order for the mutated gene sequences to survive they have to be transmitted back to the natural reservoir so they can be conserved(71). That means that as long as containment measures are put in place the mutations will "burn out." This underscores the importance of control measurements.

4.2 Infected health workers- a challenge in response to the epidemic

In response to an epidemic like the Ebola in West Africa, health workers are fundamental. Therefore, when such a substantial number of the health workforce infections and deaths occur, the response to the epidemic is weakened. This further deteriorated an already fragile health workforce (38). Health worker infections did not only threaten the ability to manage the current outbreak, but also impaired the health systems' abilities to provide future health services. When foreign health workers engaged by international organisations also became infected it contributed to weaken the response. An additional challenge is that health worker infections may contribute to increased community mistrust and therefore preventing EVD patients from seeking health services. As Forrester and colleagues explain in their Morbidity and Mortality Weekly Report (MMWR) this creates new opportunities for transmission of Ebola and further impair the capacity of the health system (53). Another aspect is that infected health workers unknowingly can transmit the disease to other patients, creating an extreme dangerous situation.

Health worker case counts declined from the autumn 2014 (Figure 3). A few events can explain this. Infection Prevention and Control strategies (IPC) strategies were lacking in the early phase of the response and weren't augmented until the second half of 2014 (49, 51, 52). Therefore, it's plausible that these measures contributed to declining case counts and has also been posed as a factor in the literature (38, 50, 52). Matanock describes in an article that overpowering infections in the staff lead to closure of health facilities. Closure of health facilities is discussed as a contributing factor to the decline of cases (50). Consequently, health services became more unavailable with fewer patients seeking help and health workers

were less exposed to transmission. Figure 3 also demonstrates a small increase of cases after January 2015. WHO discuss that a possible explanation is that as case counts in the general community apparently decreased, adherence to Personal Protective equipment (PPE) and general hygiene decreased (43).

As previously discussed, transmission of Ebola is associated with general care. This is also illustrated in the health sector were nurses as an occupational group accounted for > 50% of the infected health workers. Nurses are generally in more direct contact with their patients and consequently at higher risk for contamination.

Based on gender, a male predominance in health worker infections was noted. Furthermore, 95% of the medical workers were men, but amongst the nurses (the workforce group most affected) the men constituted 45%. In Guinea for instance, the males represented 46.4% of the total health workforce. As an occupational group, doctors constituted a larger proportion than in the two other countries. However, as Grinnell points out, this doesn't explain the whole picture because even in most of the health workforce groups, infections in the male workers were more common than in female workers (20). This is also supported by WHO findings that men disproportionally affected. The exact reasons therefore remain uncertain, and WHO highlighted the need for investigations (38).

The high infection risk that is associated with being a health worker can be explained by the fact that Ebola cases were more concentrated in health care setting than in the general community, and when precaution measures were suboptimal health workers were at significant infection risk. Hence, favourable conditions for nosocomial transmission are created and to later extent amplification of case counts.

Infections occurred more commonly in non-Ebola Treatment Units (ETUs) than in facilities dedicated to Ebola treatment. Several risk factors and determinants on different levels existed in the workplace. To review all of the identified factors is not the intention of this paper, but some factors should be addressed.

A possible explanation for the big difference in health worker infections between ETU- and non-ETU settings is that in the ETU settings administrative infrastructure (leadership, procedures regarding triage, PPE, waste management etc.) was implemented to a greater

extent than in general care facilities. Health workers also received extensive training before beginning their work in the ETUs (56). That infrastructural challenges was a common problem outside ETU settings is understandable as one cannot expect that health systems without previous experience with Ebola management to succeed on their own. Consequently, the Ministries of Health (MOHs) in the respective countries were assisted by WHO to implement sufficient systems (38). However, the responses were significantly delayed (74) and that contributed to the widespread health worker transmissions.

Ideally all patients should have been triaged, isolated and treated at dedicated Ebola facilities. Forrester and colleagues provide an example. In Monrovia, Liberia there was a dedicated ETU facility that was in close proximity to a community hospital where the emergency department served as the triage point for the ETU (53). Additionally, patients often sought care in traditional health facilities, either for EVD symptoms or other diseases. Patients were sometimes not recognized to have EVD (49, 53). Inconsistent triage systems are maybe one of the most severe shortcomings when it comes to protect health workers from the Ebola virus because the consequence is that health workers provide unprotected care to highly infectious patients.

Personal Protective Equipment (PPE) provides a physical barrier between the health worker and the infected patient, thus ensuring interruption of transmission chains. In the 2013-2016 West African Epidemic concerns regarding PPE were detected on many levels in the health care setting. Resource shortages are problematic for several reasons. Obviously, PPE cannot be used when it's lacking. Secondly shortages may lead to the reuse of already utilised equipment, as indicated in table 3. Nevertheless, the availability of PPE is in my opinion not sufficient to prevent health worker infections. Structured training on how to don, doff and general behaviour while wearing PPE is essential. For future purposes, the training should contain both theoretical and practical sessions for optimal learning. These goals are ambitious, especially in countries with pre-existing infrastructural challenges. However, such Ebola outbreaks as seen in West Africa are a danger to public health, meaning that they are of international concern, demonstrated by the declaration of The Epidemic being "a public health emergency of international concern" by WHO on August 8th 2014 (45).

One must also keep in mind the challenging conditions under which health workers worked: Just wearing PPE for a durable time in high humidity and temperature can be exhausting.

When adding long working hours, staff shortages and emotional distress it's understandable that mistakes could be made, even by adequately trained staff. Therefore, it is recommended that health workers work in pairs in ETUs. If problems occur, the “buddy” will back up their partner. The buddy also serve as an additional overseer in case the partner misses an important step (56). That this was difficult to accomplish, is understandable. As table 3 reports, staff shortages were a problem during this Epidemic. This can explain why it wasn’t always possible to work in pairs. Another aspect of this problem is that others become overloaded with work leading to exhaustion. Under such circumstances mistakes are easer made, thus providing opportunities for infection.

As Olu and colleagues discuss, the findings should provide confidence to those working in ETU facilities that protection measures put in place are effective when protocol is followed. Additionally, this may have contributed to demystify prejudices and resistance about the ETUs in the communities and that health worker infections in these facilities were uncommon (51). As an example, of the 3400 MSF employed staff, 27 acquired EVD. This number is very low compared to other institutions, indicating that MSF personnel were professional, well trained and that security is of top priority. The investigations on the MSF personnel that acquired Ebola revealed that most transmissions had occurred in the community, outside the work settings (43). This further proves that prevention measures in these treatment facilities are effective when adhered to.

As some of the findings indicate and further illustrated by the MSF workers community acquired EVD infections, it's highly expected that other health workers also contracted Ebola outside the place of work. First of all, like everyone else health workers are a part of their respective general communities. They have families and friends. They engage in local events, like funerals. Interestingly, the one report from Sierra Leone indicated that health workers were less likely to have attended funerals (50), and could partly be explained by greater awareness in health workers. Physical contact is many places part of everyday life. Finally, health workers often have a strong desire to provide care for ill relatives and colleagues. When preformed without adequate protection, a part of the health worker infections can be explained, without being able to provide with specific numbers.

4.3 Containment measures – important, but challenging

Ebola is transmitted by human-human transmission through direct contact with infested bodily fluids. Consequently, all prevention measures that are implemented in response to an outbreak are aimed at breaking these transmission chains. The importance of early detection of cases cannot be emphasized enough. If adequately conducted, early detection is followed by prompt isolation, which reduces transmission within the community. Contact tracing should always be conducted after case identification.

4.3.1 The Ebola Treatment Unit (ETU) is designed to prevent transmission

The layout of the ETU in itself is aimed at preventing human-human transmission (56) and is therefore a relevant part in IPC strategies. Figure 5 provides a graphic structure of an Médicins Sans Frotières (MSF) ETU and differs slightly from the explanation given in the text that is based on CDC standards. The greatest difference is that the MSF ETU contains three zones within the high-risk area. This difference isn't of great importance as both serve their function as isolation units.

At the triage area it is important to identify those with EVD in order to rapidly isolate them from the community, but it is also relevant to distinguish these patients from non-EVD cases. Patients without Ebola should not be hold up in these settings, as this may increase the likelihood for contamination.

Furthermore, the zones of the hospital are a contribution to limit transmission. Patients with suspected and confirmed Ebola are separated in the high-risk area. In the suspected area patients are tested for EVD and some will be negative, illustrating the importance of dividing the high-risk area in order to prevent transmission. Symptomatic EVD patients are highly contagious. The benefit of the ETU is that these highly infectious patients are located with other contagious people, thus preventing both community transmission and transmission to other patients as they cannot infect each other. Another important aim of establishing ETUs was to provide good supportive care (56). In previous epidemics with a limited number of cases, isolation and further transmission was of main priority. Due to the extent of the 2013-2016 West African Epidemic the need for treatment was addressed. By providing with fluid and electrolyte substitution, mortality was reduced from 80% to 50% (69). This is a monumental decline in deaths, illustrating the importance of this strategy in the future.

This may also encourage patients to seek these facilities. The ETUs also ensure better control over the deceased EVD patients, and important aspect, as they are highly infectious.

The unidirectional flow of both patients and employees adds another dimension to preventative measures. Movement from low-risk to high-risk area ensure that EVD positive patients don't infect non-EVD patients. Additionally as all surfaces in the high risk area should be considered as contaminated (56) a unidirectional flow of health workers prevent transmission from contaminated PPE to non-Ebola patients.

Although the physical layout of these facilities provides protection for both patients and health workers, it's only one aspect regarding the containment measures within the ETU. The importance of PPE has already been addressed. Furthermore, strict hygiene protocols are fundamental to prevent transmission, also between patients. This might be particularly important in the suspected area, where health workers potentially can transmit EVD from infected patients to non-EVD patients if hand hygiene is unsatisfactory. Other important aspects are how to obtain blood samples, how to manage waste and corpses (56). Strict adherence to protocol limits infection within the facilities.

4.3.2 Safe burials – where security and culture collides

An insight to the risk of transmission is provided for in the findings, where amplification of cases through burial ceremonies is provided for. This also illustrates the risk for contamination that is associated with deceased patients. Some of the most common practices include touching and washing of the dead body providing an enormous opportunity for transmission. The WHO guidelines are scientifically developed and based on previous field experiences (58) to prevent direct transmission. That these guidelines were met with resistance is understandable because they interfere with local customs at a very vulnerable time. Resultantly, in order for safe funerals to be conducted, response teams rely on community engagement. Therefore the necessity to obtain permission to conduct the funeral, respecting religious views/traditions and to inclusion of family members and religious leaders in the ceremony cannot be undermined. This ensures dignity for the deceased and the mourners and may contribute to reduce tension (58). Manguvo and Mafuvadze highlight the importance of targeting information campaigns towards community leaders as the people

often accept instructions given by someone that they trust (75). This should be a key strategy in future epidemics and must not be delayed.

4.3.3 Contact tracing

As presented in the material and methods the reproduction rate, R_0 provides an estimate of the number of secondary cases per infected patient in a susceptible population. Even though this number is significantly lower (45) compared to measles for instance (76) they demonstrate that transmissions will continue to occur even if one contact is missed. As illustrated by figure 5 the premise for contact tracing is case identification. The case definition is previously discussed. The process of interviewing the cases will hopefully reveal all potential contacts. Interviewing relatives or other people close to the case and/or contact may provide additional information and can be of great value. This is especially important if the patient is dead at time of identification. Subsequent questioning of the contact regarding symptoms and signs of EVD provide the opportunity to uncover a new case. Therefore, the 21 days of daily observation is meaningful as this is the incubation period for the virus. A detailed observation form is provided for in the guidelines, regarding EVD symptoms. If symptoms develop, the potential case (former contact) can be managed accordingly.

This response is highly dependent on the contact acceptance to be observed and as WHO guidelines point out that might be dependent on many different factors (55): first of all knowledge about the disease essential. Why should someone contribute to being monitored for a disease they know nothing about and sometimes even doubt that it exists. Second the stigma associated with the disease may restrict the effectiveness, also because listing of the contacts of contact may be a source of conflict in the communities. As for the burial ceremonies a key to community acceptance is to cooperate with the community and religious leaders, and highlight that the intention of this process is not only to limit community transmission, but also to provide decent medical care. As already addressed, the vast geographic distribution and population characteristics challenged contact tracing, a problem that WHO also pointed out. Finally, because of the different response partners in this outbreak different standards for contact tracing were implemented in different areas. One standard approach is ideal and can prevent loss of contacts and therefore on-going transmission (55).

4.3.4 Vaccination, where do we stand?

Vaccination has traditionally been a very important tool to prevent transmission. As this also provides with immunity of a given disease, it affects the R_0 and secondary cases may therefore be reduced. The ring vaccination trial conducted by Henao-Restrepo et al. in Guinea and Sierra Leone is a new and interesting study design that reflects the way Ebola is transmitted. Contacts and contacts of contacts were identified and eligible candidates were included in the study (61). This is a clever strategy given that people closest to a symptomatic EVD patient is at greatest risk for acquiring the disease. Randomisation is preferable when conducting medical studies, but during the study period some ethical challenges were identified, due to promising preliminary results. Consequently, the randomisation stopped and children were also included in the study. When no cases of EVD were detected after 10 days in the immediate vaccination group, the vaccine efficacy was calculated to 100%. However, the number of patients in the control group was low, and could affect the efficacy results.

According to the Strategic Advisory Group of Experts on Immunization (SAGE) 12 different vaccine candidates for Ebola are in a trial phase (77). However, according to them and Henao-Restrepo et al. the "Ebola, ça suffit!" trial is the only one demonstrating a clinical effect of an experimental Ebola vaccine (61, 77). Although not being a part of the study some evidence of indirect immunity was provided for. The authors argue that the still experimental vaccine contributed to containment of the 2013-2016 Epidemic (61). Consequently, it is SAGE's recommendation that the experimental vaccine is to be used in future Zaire Ebola epidemics with ring vaccination as standard (77). The latest outbreak of Zaire Ebola virus was declared in DRC on May 8th 2018 and WHO is in collaboration with the MOH and MSF implementing the experimental vaccine as an IPC strategy (62). Even though the vaccine is still experimental it has the potential to prevent community transmission, provide protection to health workers and maybe even discourage use of the virus in biological warfare. It should be underscored that even though the vaccine shows promising results it must not be a replacement of other, validated IPC measures, but serve as a supplementation.

What the study by Henao-Restrepo and colleagues fail to provide is an estimate immunogenicity of the vaccine due to a decision of not to collect biological material. This is attributable to difficulties with the implementation of the trial (61).
However, a double-blinded, placebo-controlled dose-response study by Heppner and colleagues published in the Lancet (78), provide evidence that binding an neutralizing

antibodies still was maintained after 1 year. Even though these are promising results, it is important to distinguish between antibody detection and protection against the disease. In other words: biochemical immunity and protective immunity is not the same. What implication viral mutation rates had or will have on vaccine efficacy/development in the future remains uncertain, but should not be neglected. Another limiting factor is that the recommendations only are applied for Zaire Ebola virus. As other species of Ebola traditionally has caused epidemics (table 2) this should also be expected in the future. This highlights the need for further research. An aspect that must not be disregarded is that in order to conduct the vaccination, the vaccine must be transported to the current area. The difficulty in transporting it is demonstrated by the current 2018 outbreak in DRC where the epicentre is a remote area 15 hours by motorbike from the closest town. This is further augmented, as the vaccine has to be stored at minimum -60ºC (79). This highlights that even though an experimental vaccine is proven effective, the availability to the people can be restrictive.

4.4 Thesis strengths and limitations

Due to the recentness of The West African Ebola Epidemic from 2013-2016 a challenge to the research was that comprehensive analyses of The Epidemic have not yet been completed, as the trauma of The Epidemic is still raw in memory. As such, in the early phase of my research, I realised I needed to develop my own parameters instead of following those in the existing literature. Furthermore, due to the complexity of The Epidemic it was not possible to review all events and problems that occurred during that time. Consequently, this thesis only covers three main aspects of The Epidemic, and not the full picture. The thesis covers a snapshot of some of the events. As new knowledge continually becomes available, the picture might look different in the future.

As a consequence of The Epidemic's many challenges it was found appropriate to review several aspects. In retrospect, three main topics might be considered as too extensive for this thesis. Since there were several problems that were to be reviewed, it was found appropriate to preform separate searches for each problem that was to be highlighted. An ideal approach when constructing literature studies is to construct a wide-range search matrix for systematic searches. The chosen method was not ideal, but seemed most suitable within the bounds of this project. This could mean that potential relevant articles were not identified. However, it cannot be guaranteed that a more systematic search strategy would provide another result.

For certain parts of the paper, PubMed was the main search engine. This could be a limitation in itself as this excludes potentially relevant articles in other databases. Some of the search results included review articles that were found to be relevant for this thesis. Although such articles are not original research, they provide a valuable insight to certain topics. Such articles are often written by people considered experts in their fields and they must be read critically as they can include the author's personal opinion. A way to ensure that they are of decent quality is to review the sources these articles are based on. The findings in these articles are also supported by findings elsewhere in the literature. Additionally, some sources were also retrieved after screening reference lists. This may be a result of an unsystematic search or too narrow search terms. In addition, some sources are based on personal communication. Even though some of these findings might be challenging to reproduce, it is my conclusion that they are representative.

Some parts of this thesis are based on a limited amount of sources, primarily WHO documents and CDC training documents. Although it would be ideal to provide a wider range of sources to ensure validity of the findings, documents and guidelines published by CDC and WHO should be considered of high enough quality.
A central question regarding the epidemiological data is its accuracy. As this Epidemic was an international emergency other measures than epidemiological research were prioritised. It should be noted that the VHF database on case numbers were to a certain extent incomplete with underreporting of numbers and clinical data. With regard to infected health workers, different definitions of what constituted a health worker were used, and in some cases not all categories were considered as such. This may also have affected the data.

Furthermore, the included articles that identified possible exposures and risk factors for infection were of retrospective nature. Retrospective identification of possible exposures and risk factors can create opportunities for "recall bias", and especially under the challenging circumstances of The Epidemic and the stigma of being infected. However, many of the same problems were identified throughout the different articles, indicating that the findings have substantive value.

5. Conclusion

The findings in this thesis have not been able to provide new knowledge on the 2013-2016 West African Ebola Epidemic, but has attempted to provide a review of some distinguishing epidemiological features, features of infected health workers and contributing factors and key elements to stopping such an epidemic.

5.1 Ebola: Old virus in a new setting

Up until the 2013-2016 West African Ebola Epidemic 23 identified outbreaks have been identified in Central Africa. Several different strains have been identified, with varying Case Fatality Rates. Bats have been identified as the likeliest animal reservoir for Ebola where the infection persists, but does not cause clinical disease. Occasionally, a pathogen spill-over into a human population takes place. The West African Ebola Epidemic was the first of its nature to occur in this part of Africa. Zaire Ebola Virus was identified as a causative agent. It is likely that the virus has circulated in this region prior to the outbreak. Fruit bats are common in this region and it has experienced significant forest loss. The exact role for this in pathogen spill-over into the human population is undetermined, but may have lead to closer and more frequent encounters between bats and humans. The geographic origin in itself may have contributed to the spread due to several reasons. This was a viral disease new to the areas. It wasn't considered a likely diagnosis and was masked by other endemic diseases. Correct identification of the virus was severely delayed, thus facilitating undetected spread throughout the populations. The health system had no experience with managing cases. The epicentre in Guinea was located in close proximity to the borders of Liberia and Sierra Leone. The populations in these three countries are highly mobile and convenient access existed both across the borders and between rural areas and large cities. This facilitated dissemination of the disease. The introduction of the virus to cities with multi-million inhabitants enabled for the first time ever, transcontinental spread. The first transmission chains through family members reveal that Ebola is a virus that through caregiving. Some case amplification was seen in health facilities, but a significant increase of cases occurred through burial ceremonies.

5.2 Impact on the health workforce

During the West African Epidemic a substantial number of health workers were infected and died and compared to the overall population they were significantly at higher risk. As for the general population the findings indicate that transmission is associated with general care giving. Most infections occurred outside dedicated Ebola Treatment Units (ETUs). This indicates that the training, prevention measures and overall protocols in ETU settings work to prevent health worker infections. In hospital settings, other than ETUs several risk factors and shortages in prevention measures have been identified. This provided massive opportunities for infections in the workplace. Also, health worker infections occurred in the communities. As there were many possible exposure opportunities, to establish the exact settings for transmission is difficult. Health workers are essential when building a response system to stopping an outbreak. High numbers of infected health workers can lead to amplification of cases, undermine the overall response to such epidemics and impair future health services. For future purposes sufficient training, guidance and protective equipment in addition to clearly defined triage systems for identification of cases will be essential to prevent health workers from acquiring EVD.

5.3 Containment measures

In order to contain an outbreak early identification of cases is essential. All successive measures aim to prevent direct human-human transmission. Establishment of dedicated Ebola Treatment Units that were designed with separate areas for triage, suspected and confirmed cases and with a unidirectional flow for patients and health workers. This design prevented transmission both between patients and to health workers. Strict adherence to guidelines for Personal Protective Equipment and hygiene protocols are fundamental for the ETU to serve as intended. The ETUs did not only as isolation units, but were also a facility were good supportive care could be received.

Contact tracing is a key in containing an Ebola outbreak. All contacts of a case should be identified through thoroughly conducted interviews. Even if one contact is missed new chains of transmission will continue to occur. The contact is followed up for 21 days and asked daily about possible EVD symptoms. If symptoms develop, the person can be managed immediately. During the West African Ebola Epidemic this response was challenged as a consequence of the substantial number of infected, vast geographic spread: both to multi-

million cities and across national borders. As contact follow-up is highly dependent on the persons willingness to being monitored this may have added another dimension to challenges in this response. As a consequence of the massive amplification of cases through traditional burial ceremonies, the West African Ebola Epidemic illustrates the importance of conducting safe burials. The WHO guidelines provide with a detailed step on how this ideally should be conducted, but this response was challenged due to the interference with local cultural customs.

Vaccination has traditionally been an important tool to prevent transmission as it can provide immunity. During the 2013-2016 West African Epidemic a clinical trial on the efficacy of the experimental rVSV-ZEBOV vaccine showed promising results. More research on this vaccine in needed before licencing. Despite this, the vaccine has the potential to serve as a containment measure in future epidemics.

5.4 The future perspective

The emergence of Ebola in Guinea illustrates that the whole West African region should be prepared for future outbreaks. Bats are common in this region and as long as the animal reservoir exists future outbreaks are inevitable. To eradicate bats as a strategy to prevent future outbreaks is an impossible mission. Therefore, strategies to limit outbreaks are an expedient approach. The 2013-2016 West African Epidemic highlights the importance of having knowledge and experience with such outbreaks. A lesson from this Epidemic is to always consider EVD as a differential diagnosis when patients present with mysterious symptoms, thus ensuring rapid identification of correct agent. The fear of Ebola might be a greater danger than the virus itself. Lack of knowledge is an important fear driver. An important focus area in preparedness for future outbreaks in exposed areas should entail general EVD education. All community members should be informed, but community and religious leader should especially be enlightened, as they are respected and trusted in the communities and can reach out to their members.

Ebola will always exist, but with knowledge and experience epidemics can be limited.

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9. Appendix

9.1 Summary of literature evaluations (GRADE)

<table>
<tr><td colspan="3">Reference:
WHO. Health worker Ebola infections in Guinea, Liberia and Sierra Leone 2015 [16]. Available from: http://www.who.int/csr/resources/publications/ebola/health-worker-infections/en/. WHO reference number WHO/EVD/SDS/REPORT/2015.1</td><td colspan="2">Design: Case series
Level of scientific evidence: III
Grade: 2</td></tr>
<tr><td>Aim</td><td>Materials and method</td><td>Results</td><td>Discussion</td></tr>
<tr><td>To describe and characterize health worker infection outcomes, and to quantify the risk of infection in health workers.

Conclusion
Depending on the helath profession, the risk was between 21 to 32 times higher in health workers compared to non-health workers ≥ 15 years of age. While the risk of infection among those selected health workers is very high, is is however, much lower than the risk previously reported.

Countries
Guinea, Liberia and Sierra Leone

Years Data Collection
2014-2015</td><td>Data source:
The Viral Haemorrhagic Fever (VHF) database (comprised of the national VHF databases from Guinea, Liberia and Sierra Leone).

Population:
Registered cases of EVD in Guinea, Liberia and Sierra Leone from January 1st 2014 to March 31st 2015.
Excluded:
- Suspected cases (only included confirmed and probable cases)
- Age < 15 years

Exposure:
- Health workers/non-health workers.
- Country: Guinea, Liberia, Sierra Leone
- Sex: Female/male.
- Age-group: 15-29 years, 30-44 years, ≥ 45 years.
- Hospitalization: Yes/No
- Final outcome: Alive/Dead

Statistical analyzes:
Chi-square tests.</td><td>Health workers accounted for 3,9 % (815/20 955) of all confirmed and probable cases of EVD reported in the study period. It decreased from 12 % in July 2014 to 1 % in February 2015.

Depending on the health profession, the risk was between 21 to 32 times higher in health workers compared with non-health workers.

61 % of health workers infections were in males.

Nearly 50 % of all EVD infections in health workers occurred in those ages between 30 and 44 years old.</td><td>Sjekkliste:
• Was the study based on a random sample from a suitable patient group? Yes.
• Was it ensured that the sample was unselected?? No, great uncertainty about the registration in the database.
• Were the inclusion criteria clearly defined? Yes.
• Was the response rate high enough? Not relevant.
• Were all the patients in the sample in same stage of disease? All cases with same disease.
• Was the follow-up of patients sufficient (type/dimension/time) to display the end-points? Not relevant.
• Were the criteria to validate the end-points objective? Validation uncertain.
• When comparing case-series, were the series adequately described and the allocation of the prognostic factors described? Unclear.
• Was the data registration prospective? No.

Strength
- Included cases in three countries with widespread and intense transmission, and a relatively large number of cases (when the diagnosis is taken into account) when suspected cases excluded

Weakness
- Minimal information about how the registration in the database is done. For health workers: Reported by the case themselves, and we don´t know if the infection was acquired with or without linkage to care provision.
- Limited clinical data (under-reporting, duplications, missing and incomplete data, all health workers might not have been recorded as health workers)
- Some uncertain diagnoses since probable cases included, and a significant number of health worker infections with unknown status among the suspected cases.
- Analyzes: Only calculated for selected professions where data were more complete.</td></tr>
</table>

Reference: Senga M, Pringle K, Ramsay A, Brett-Major DM, Fowler RA, French I, et al. Factors Underlying Ebola Virus Infection Among Health Workers, Kenema, Sierra Leone, 2014–2015. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2016;63(4):454-9.	**Design: Case series**	
	Level of scientific evidence	III
	Grade:	2

Aim	**Material and methods**	**Results**	**Discussion**
To examine facort associated with Ebola virus exposure and mortality in HWs in Kenema District, Sierra Leone **Conclusion** The cluster of HW EVD cases in Kenma District is one of the largest ever reported. Most HWs with EVD had potential virus exposure both inside and outside of hospitals. Prevention measures for HW´S must address a spectrum of infection risks both formal and informal care settings as well as in the community. **Country** Sierra Leone **Year data collection** 2014-2015	**Data source** Viral hemorrhagic fever database (maintained by Sierra Leone Ministry of Health and Sanitation). For HWs database was supplemented with contact tracing records to obtain additional information about contacts. Hospital records, burial logs and public obituaries were also included. **Population** Registered cases of suspected, probable and confirmed EVD cases in HWs in Kenema District. Data for non-HWs were included for comparison HW-definition: anyone who worked in a healthcare facility or engaged in healing practices (eg. traditional healers) and clinical staff as persons who have traditional patient-care roles and routinely have direct contact with patients (eg. doctors, nurses, and laboratory technicians *Exclusion criteria:* persons <18 years and cases that did not meet WHO definition for EVD **Exposure** • HWs/non-HWs • Sex: male/female • Age <45/≥45 years • Reported contact with case of EVD (incl. Type of contact) • Time to symptom presentation: ≤7/>7days **Statistical analysis:** For categorical data: $\chi 2$. For continuous variables: t-test To estimate ORs for associations between potential risk factors for EVD and deaths univariate and multivariable logistic regression models were used with 95% CI. Variables that were significant in univariate analysis were evaluated in multiple logistic regression models, while retaining biologically relevant variables. P values of <.05 were considered to indicate statistical significance	In study period 600 cases of EVD originated in Kenema district, including 92 (15%) HWs, 66 (72%) of whom worked at KGH, 18% worked at other non-ETU facilities 18 of 62 (29%) worked in the ETU developed EVD, compared with 48 of 83 (58%) who worked elsewhere in the hospital. 13% of HWs with EVD reported contact with EVD patients, 27% reported contact with other infected HWs. HWs were significantly more likely to identify prior contact with someone with EVD (42% vs 24%, respectively; OR, 2.9 [95% CI, 1.7–5.0]). The number of HW EVD cases at KGH declined roughly 1 month after implementation of a new triage system at KGH and the opening of a second ETU within the district. The case fatality ratio for HWs and non-HWs with EVD was 69% and 74%, respectively.	**Check list:** • *Was the study based on a random sample from a suitable patient group?* Yes. • *Was it ensured that the sample was unselected?* No, great uncertainty about the registration in VHF database, burial logs and public obituaries and how these were accessed. • *Were the inclusion criteria clearly defined?* Yes. • *Was the response rate high enough?* Not relevant. • *Were all the patients in the sample in same stage of disease?* All cases with same disease. • *Was the follow-up of patients sufficient (type/dimension/time) to display the end-points?* Not relevant. • *Were the criteria to validate the end-points objective?* Validation uncertain. • *When comparing case-series, were the series adequately described and the allocation of the prognostic factors described?* Uncertain. • *Was the data registration prospective?* No. **Strengths** • Describes one of the largest clusters of HW infections ever reported • Access to multiple data sources **Limitations** • Retrospective collection on possible HW exposures – not all cases were interviewed • Undetermined whether HW contact with EVD patients was protected or unprotected and if breaches in protocol occurred-cannot make conclusion regarding PPE /IPC measures • Broad case definition of HW • Limited clinical data available • Data on HW infection may have been more thoroughly recorded than for non-HWs – confounding factor

Reference: Heppner DG, Jr., Kemp TL, Martin BK, Ramsey WJ, Nichols R, Dasen EJ, et al. Safety and immunogenicity of the rVSVG-ZEBOV-GP Ebola virus vaccine candidate in healthy adults: a phase 1b randomised, multicentre, double-blind, placebo-controlled, dose-response study. The Lancet Infectious diseases. 2017;17(8):854-66.	**Design: RCT**	
	Level of scientific evidence	Ib
	Grade:	3

Aim	**Materials and Methods**	**Results**	**Discussion**
To Assess the safety and immunogenicity of rVSVΔG-ZEBOV-GP **Conclusion** Local and systemic adverse events induced by vaccine was of early onset, mild-moderate, well tolerated, transient and dose-dependent. Delayed self-limited arthritis in vaccines was unrelated to dose Dose effect was seen at onset and durability of binding and neutralising antibodies manintained at day 14-day 360 Binding and neutralisisng antibodies sustained at all vaccine doses for min. 1 year post immunisation. The immunogenicity results support selection of the 2 × 10^7 PFU dose. **Country** USA **Year data collection** 2014-2015	**Study design:** Phase 1b double blind, placebo-controlled, dose-response study **Inclusion/exclusion criteria** Participants: healthy adult men, non-pregnant, non-lactating women 18-60 years old Any medical condition that might increase risk of participation of the participants or their contacts, or confound interpretation of vaccine safety and immunogenicity. Full list of inclusion and exclusion criteria available in appendix. **Randomisation:** N= 513, in two separate cohorts. Cohort 1: N= 256 assigned to receive $3x10^3$, $3x10^4$, $3x10^5$ or $3x10^6$ PFU doses of the vaccine (N=64 each group) N=74 received placebo. Cohort 2: N= 162 received $3x10^6$ (N=20) $9x10^6$ (N=47), $2x10^7$ (N=47) or $1x10^8$ (N=48) PFU doses of vaccine, N=20 received placebo. Participants were centrally allocated to vaccine groups or placebo through computer-generated randomisation list. All study personnel remained blinded throughout the study. **Outcome** Primary safety outcome: incidence of adverse events within 14 days in all randomly assigned participants Primary immunogenicity outcome: Zaire Ebola virus-specific antibody rensponses at day 28 by dose group. **Statistical analysis:** Safety analysis was based on modified intention to treat population (vaccinated and placebo) Immunogenicity was analysed in per-protocol population (on day 0 and day 28) Seroconversion for IgG ELISA endpoint tire: ≥1:200 and > x4 pre-vaccination titre. Seroconversion for PRNT60: endpoint tire ≥ x4 compared with pre-vaccination titre. Geometric mean titres and 95% CI for IgG ELISA and neutralising antibodies. Non-transformed antibody titres were compared between the different vaccine doses groups using the non-parametric Wilcoxon rank sum test. Prespecified test of linear trend of immune response increasing with dose was done with method by Rom and colleagues.	• Most adverse events occurred in the first day after vaccination, mild-moderate in intensity, short duration and more frequent at high vaccine doses • At $2x10^7$ PFU doses versus placebo most adverse local events within 14 days were: arm pain (57.4% vs 7.4%), local tenderness (59.6% vs 8.5%) Common systemic event were: headache (46.8% vs 27.7%), fatigue (38.3% vs 19.1%), myalgia (34.0% vs 10.6%), subjective fever (29.8% vs. 2.1%), shivering/chils (27.7% vs 7.4%), sweats (23.4% vs 3.2%), joint aches and pain (19.1% vs 7.4%), objective fever (14.9% vs.1.1%) and joint tenderness or swelling (14.9% vs 2.1%) • Self-limited, post vaccination arthritis occurred in 4-5% of vaccines vs 3.2% of controls. No apparent dose relationship • Post-vaccination dermatitis in 5.7% of vaccines vs 3.2% of controls • Antibody responses were observed in most participants by day 14. • IgG and neutralising antibody titres were dose-related (p=0.0003 for IgG ELISA and p<0.0001 for the 60% plaque-reduction neuralisations test by linear trend) • On day 28 at the $2x10^7$ PFU dose the geometric mean IgG ELISA endpoint titre was 1624 (95% CI 1146-2302) and seroconversion was 95.7% (95% CI 85.5-98.8), the geometric mean neutralising antibody titre by PRNT 60 was 250 (176-355) and seroconversion was 95.7% (85.5-98.8). • These robust immunological responses were sustained for 1 year.	**Check list:** • *Is the purpose of the study clearly defined? Yes* • *Was the sample allocated to the different groups using a randomisation procedure*? Yes • *Were all participants accounted for at the end of the study?* Yes • *Were participants and personnel blinded?* Yes • *Were the differences between the groups at the beginning of the study?* More men than women in study, other baseline characteristics were similar across groups • *Was the follow-up of both groups identical?* Clinical assessments for cohort 1 and 2 preformed on different days following vaccination. • *What were the results?* rVSVΔG-ZEBOV-GP was well tolerated and stimulated a rapid onset of binding and neutralising antibodies, which were maintained through to day 360. The immunogenicity results support selection of the 2 × 107 PFU dose. • *Are the results transferrable to clinical practice?* Study conducted in USA under non-epidemic conditions. Thus, outcomes may differ. • *Were all outcomes measured?* Yes • *Do the benefits outweigh the disadvantages/costs?* Yes **Strengths** -Study conducted under randomised circumstances - First comprehensive study that reported 360 days of data on safety and immunogenicity of the rVSVΔG-ZEBOV-GP vaccine. **Weaknesses** - Follow up on solicited adverse events were collected for 14 days for cohort 1 and for 56 days in cohort 2 → lower sensitivity for capturing post-injection event in cohort 1 vs 2. -Absence of cellular and innate immune studies. The immunological correlates of protection induced by the vaccine are not known.

Reference: Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ca Suffit!). Lancet (London, England). 2017;389(10068):505-18.	**Design: RCT**	
	Level of scientific evidence:	**Ib/IIa**
	Grade:	**2**

Aim	Material and Methods	Results	Discussion
To assess the efficacy of the rVSV-ZEBOV vaccine for the prevention of Ebola virus disease in human beings **Conclusion** The results add weight to the interim assessment that rVSV-ZEBOV offers substantial protection against Ebola virus disease. **Countries** Guinea, Sierra Leone **Year of data collection** 2015-2016	**Study design:** Open-label, cluster-randomised ring vaccination trial. **Recruitment of the study population:** After confirmation of a case of EVD enumeration on a list a ring (cluster) of all their contacts and contact of contacts. Contacts: Individuals who, within the last 21 days, lived in the same household, were visited by the index case after the onset of symptoms or were in close physical contact with the patient´s body or body fluids, linen or clothes. Contacts of contacts: Neighbours, family or extended family members living within the nearest geographical boundary of all contacts, plus household members of any high-risk contacts. *Exclusion- criteria for contacts*: History of EVD, age <18 years old, pregnancy/breastfeeding, history of administration of other experimental treatments during past 28 days, history of anaphylaxis to a vaccine or vaccine component or serious disease requiring confining to bed or admission to hospital by time of vaccination. **The study population and randomization:** Randomly assigned clusters (1:1) to either 1) immediate vaccination or 2) delayed vaccination (after 21 days). 476 confirmed cases of EVD. 117 clusters defined. 98 clusters randomised, 19 non-randomised. Randomised group: 51 clusters immediate vaccination (4539 contacts and contacts of contacts) where 2219 were vaccinated. 47 clusters delayed vaccination (4557) contacts and contacts of contacts) with 940 individuals vaccinated. Non-randomised group: 1677 individuals vaccinated. **Outcome:** Prespecified primary outcome was laboratory confirmed case EVD with onset 10 days or more from randomisation. All contacts are monitored at home by members of the Ebola response team for 21 days after their last known exposure to the case. **Statistical analysis:** Vaccine efficacy: VE=1-è where è=ë1/ë0 is the hazard ratio of ë1 (the hazard of disease for eligible and vaccinated individuals in a ring who receive immediate vaccination) and ë0 (hazard of disease for eligible individuals in a ring who receive delayed vaccination. Hazard ratio was estimated using Cox proportional hazard regression model.	No cases of EVD occurred 10 days or more among randomly assigned and contacts of contact in immediate cluster. 16 cases of EVD (7 clusters affected) among all eligible individuals in delayed clusters. Vaccine efficacy: 100% (95% CI 68.9-100.0 p=0.0045) Evidence from all 117 clusters (included the non-randomised clusters) showed that no cases of EVD occurred 10 days or more after randomisation among all immediately vaccinated contacts and contacts of contacts vs. 23 cases (11 clusters) among eligible contacts and contacts of contacts in delayed plus all eligible contacts and contacts of contacts never vaccinated in immediate clusters. Estimated vaccine efficacy: 100% (95% CI 79.3-100.0 p=0.0033)	**Checklist:** • *Is the purpose of the study clearly stated?* Yes. • *Was the sample allocated to the different groups using a randomisation procedure*? Yes. • *Were all participants accounted for at the end of the study?* Yes. • *Were participants and personnel blinded?* No, not possible, as this was an open-label study. • *Were the differences between the groups at the beginning of the study?* Some differences: Time to cluster definition was shorter on the immediate vaccination group, had also more high-risk contacts reported. • *Was the follow-up of both groups identical?* Yes, rates of participant compliance for all visits roughly 90 % for all visits in both groups, but the monitoring at home poorly described. • *What were the results?* Vaccine efficacy 100%. • *Are the results transferrable?* Ring vaccination with an effective vaccine can contribute as a control strategy for future outbreaks of Ebola virus disease. • *Were all outcomes measured?* Yes. • *Do the benefits outweigh the disadvantages/costs?* Yes. **Strengths:** - Generated meaningful data for vaccine efficacy without denying comparator group vaccination. **Limitations** - Relatively small study size (true vaccine efficacy may be lower) - Study conducted when incidence of EVD was low and declining. - Recruitment of the contacts based on what the cases say/remember. Selection bias? - The proportion of contacts vs. contacts of contacts the same in the both groups? A larger proportion of contacts, with a higher risk of being transmitted, in the delayed group? - The incubation period varies from 2-21 days, and it is impossible to say if a contact was in contact with the case before or after the case was infected. Confounding? - Not blinded: More aware of symptoms in the delayed group?

Reference: Baize S, Pannetier D, Oestereich L, Rieger T, Koivogui L, Magassouba N, et al. Emergence of Zaire Ebola virus disease in Guinea. The New England journal of medicine. 2014;371(15):1418-25.	**Design: Cross-sectional study**	
	Level of scientific evidence:	**III**
	Grade:	**2**

Aim	**Material and methods**	**Results**	**Discussion**
To conduct epidemiologic investigation and virologic analysis of blood samples from patients with symptoms of mysterious disease. **Conclusion** The study demonstrates the emergence of a new EBOV strain in Guinea. Epidemiologic investigation linked the laboratory-confirmed cases with the presumed first fatality of the outbreaks in December 2013. **Country** **Guinea** **Years of data collection** 2014	**Patients:** Blood samples were obtained from 20 patients hospitalized in the study countries because of fever, diarrhoea, vomiting or haemorrhage (suspected of being infected). Demographic and clinical data for the patients were provided on the laboratory request forms. **Virus detection:** Blood samples analysed in biosafety 4 laboratories in Lyon, France and Hamburg. Conventional Filoviridae-specific RT-PCR assays targeting a conserved region in the L-gene, in addition to EBOV-specific real-tome RT-PCR assays targeting the glycoprotein or nucleoprotein gene. Complete EBOV genomes were sequenced with the use of conventional Sanger techniques. Specimens from Electron microscopy were additionally used for two patients. **Epidemiologic investigations:** Gathered data on possible transmission chains from hospital records and through interview with patients.	Samples from 15/20 patients positive on conventional L gene PCR assay and real-time assays. EBOV identified in serum from 1 patient on electron microscopy, 5 patient samples revealed EBOV from cell cultures. Three patient samples were completely sequenced. The Guinean EBOV strain showed 97% idenity to EBOV strains from the Democratic Republic of Congo and Gabon. Confirmed cases originated from hospitals in Guéckédou, Macenta, Nzérékoré, and Kissidougou prefectures Index case was a 2-year old child who Meliandou in Guéckédou prefecture in late December 2013. Patients S2 (sister), S3 (mother) and S4 (grandmother) died in January. Patient S14 was a health worker and triggered the spread to Macenta, Nzérékoré, and Kissidougou in February 2014. 13 of the confirmed cases could be linked to four different clusters, with all these clusters being linked to several deaths in the villages of Meliandou and Dawa between December 2013 and March 2014. Before end of March 2014, 111 clinically suspected cases and 79 deaths had been recorded in the prefectures of Guéckédou, Macenta, and Kissidougou. The high degree of similarity among the 15 partial L gene sequences + three full length sequences + epidemiologic links between cases suggest a single introduction of virus into human population The phylogenetic analysis established a separate clade for the Guinean EBOV strain. This strain has evolved in parallel with strains from DRC and Gabon from a recent ancestor and has not been introduced from latter countries to Guinea.	**Checklist:** • *Was the population where the samples were obtained from clearly defined?* No, only that the 20 hospitalized patients who were suspected of being infected. • *Was the sample representative for the population?* Uncertain. • *Is it accounted for (and how) whether the respondents differed from the non-respondents?* Probably not relevant, but not presented. • *Is the response rate high enough?* Not relevant (?). • *Was the collection of data standardised?* Probably, but the blood samples were analysed in different laboratories in Lyon, France and Hamburg. • *Were the criteria for evaluation of outcome objective?* Yes. • *Were the methods used in the analysis of data adequate?* Yes. **Strengths** - Was able to detect EBOV at the set point in time. **Limitations** - Selection of cases uncertain/not adequately described - Data on transmission chains collected retrospectively in unstandardized fashion, providing opportunity for cases being missed. - Lack of understanding of the evolutionary rate of EBOV in nature. Cannot determine the timing and its phylogenetic origin. - Analyses done in different laboratories (differences?)