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Institute of Hygiene and Tropical Medicine

Comparison of the initial Ebola virus disease symptoms and subsequent sequelae of 10 survivors in the Koinadugu district of Sierra Leone during the 2014-2015 outbreak

(a pilot study)

Ana Sofia Rodrigues

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Under the orientation of Prof. Dr. Jaime Nina

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Abstract

The 2014-2015 West Africa Ebola Outbreak was the largest the World has ever seen. It started in December 2013 and was left unnoticed for 3 months, allowing for the virus to keep spreading uncontrollably and for the outbreak to keep escalating until it was declared an International emergency in August 2014.

Both short and long term complications have been reported on EVD survivors, ranging from physical to psychological and social and, in addition, the persistence of EVD in selected body compartments of the survivors (i.e.: semen) poses a great risk of reintroduction of the virus in areas where transmission has previously been eliminated.

This study aimed to identify the symptoms presented by 10 non-randomized EVD survivors both during the acute stage of the disease and months after recovery and understand if there was any relation between these two stages. The most common symptoms recorded during the active stage of EVD were weight loss, joint pain and fever; and months after were headache, fatigue, weakness and back pain. Sixty per cent of survivors presented months after recovery with one or more of the symptoms they had during the acute stage of the disease, being headache the most common symptom to persist, followed by weakness. However, all survivors presented with one or more symptom months after recovery, regardless of the symptoms existing during the acute stage of the disease.

The pathogenic and biological events that lead to the development of PEVDS are still unclear and more studies still need to be done on that subject. However, taking in consideration a symptomatic approach, this particular study concludes that the severity of the disease in its acute stage doesn't seem to be associated with the severity of the sequelae, also known as post-EVD syndrome.

Keywords: Ebola virus disease, Ebola sequelae, post-Ebola virus disease syndrome, outbreak, Sierra Leone.

Sumário

A epidemia pelo vírus Ébola que devastou a África Ocidental em 2014-2015 foi a maior que o Mundo testemunhou até hoje. Começou em Dezembro de 2013 e permaneuceu indetectável durante 3 meses, permitindo que o vírus se continuasse a espalhar de forma descontrolada e para a epidemia escalar até ao ponto em que foi declarada uma emergencia internacional em Agosto de 2014.

Consequências a curto e longo prazo têm sido documentadas em sobreviventes, variando desde físicas, a psicológicas e sociais. Além disso, a permanência do vírus em determinados compartimentos biológicos de sobreviventes (ex: sémen) colocam os países em alto risco do vírus voltar a ser introduzido em comunidades onde este já foi eliminado.

Este estudo procurou identificar os sintomas de 10 sobreviventes da doença pelo vírus Ébola, escolhidos de forma não aleatória, tanto no momento em que estavam com a doença na sua fase activa como nos meses de convalescença, e verificar se haveria alguma relação entre os dois. Os sintomas mais comuns durante a fase activa da doença foram perda de peso, artralgia e febre; e nos meses de convalescença foram cefaleias, fadiga, astenia e lombalgias. Sessenta por cento dos sobreviventes apresentavam na fase de convalescença, um ou mais dos sintomas que tinham durante a fase activa da doença, sendo as cefaleias o sintoma mais comum a persistir, seguido de astenia. No entanto, todos os sobreviventes apresentavam no mínimo um sintoma meses após a fase activa da doença, independentemente dos sintomas que haviam desenvolvido na fase activa.

Os eventos biológicos e patogénicos que estão envolvidos no desenvolvimento do síndrome pós-Ébola ainda não são claros e mais estudos são necessários nesta área. No entanto, e tendo em consideração uma abordagem sindromática, este estudo em particular conclui que a gravidade da doença pelo vírus Ébola na sua fase aguda não parece estar associada com a gravidade das sequelas apresentadas, também conhecidas como síndrome pós-Ébola.

Palavras-chave: Doença por virus Ébola, sequelas do Ébola, síndrome pós-ebola, surto, Serra Leoa.

Table of contents

List of figures

List of abbreviations

BBC – British Broadcast Company

CCC – Ebola Community Care Centres

CDC – Centers for Disease Control and Prevention (United States of America)

CNS – Central Nervous System

CSF – Cerebrospinal fluid

DFID – Department for International Development

EBOV – *Ebolavirus*

EVD – Ebola Virus Disease

ETC – Ebola Treatment Centre

HC – Ebola Holding Centre

IPC – Infection prevention and control

MdM – Médicos del Mundo

MoSH – Ministry of Health and Sanitation

MSF – Médicienes sans Frontiéres (Doctors Without Borders)

NERC – National Ebola Response Centre

NGO – Non-Governmental Organization

ORS – Oral rehydration solution

PEVDS – Post-Ebola virus disease syndrome

PPE – Personal Protective Equipment

ROA – Regional office for Africa

UK AID – United Kingdom Aid

UN – United Nations

UNMEER – United Nations Mission for Ebola Emergency Response

US FDA – Food and Drug Administration of the United States

WASH – Water, Sanitation and Hygiene

WHO – World Health Organization

1. INTRODUCTION

The Ebola Virus Disease (EVD) Outbreak that occurred in West Africa during 2014 and 2015 was the largest Ebola epidemic the World has ever known. I got the chance to go to Sierra Leone, the country with the highest number of reported cases, during the months of August to October 2015 as nurse working for a Spanish Non-Governmental Organization – Médicos del Mundo – and work at an Ebola Holding Centre in Kumala, Koinadugu district. By that time, this area in particular hadn't seen an Ebola case in over 100 days but there was an existing high number of survivors, which led me to this dissertation where I will compare the symptoms these survivors had upon admission to the Holding Centre (EVD clinical features) and the complications they had in the convalescence stage (post-EVD syndrome) to see if there is any correlation between the two.

1.1. Ebola virus disease

The Ebola Virus Disease is a hemorrhagic fever caused by a virus from the *Filoviridae* family, *Ebolavirus* (EBOV) genus, that can infect only a few species of mammals, such as humans, bats, monkeys and apes.[1,3]

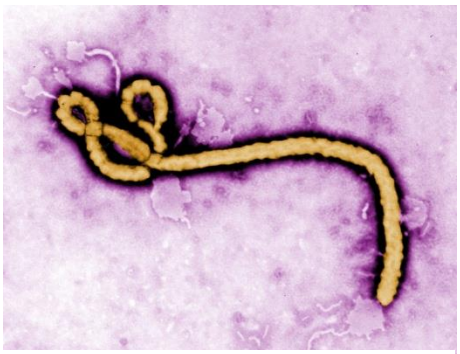

Fig. 1 The *Ebolavirus*. http://www.cdc.gov/media/dpk/2014/images/ebola-outbreak/img8.jpg accessed 30 December 2015.

Within the EBOV genus there are five different species, four of these capable of causing disease to humans – Ebola virus (*Zaire ebolavirus*), Sudan virus (Sudan *ebolavirus*), Taï Forest virus (*Taï Forest ebolavirus*, formely known as *Côte d'Ivoire ebolavirus*), and Bundibugyo virus (*Bundibugyo ebolavirus*) – all found in the African continent.[1]

The natural reservoir for this virus is still unknown. However there is evidence that several mammal species can harbour and transmit the virus and several bat species have been found to carry filoviruses[2], leading researchers to believe that 1) the virus is animal-borne; 2) that the bats are the most likely reservoirs[1] (specifically the fruit bats

from the *Pteropodidae* family[4]); and 3) that the first patient becomes infected through contact with an infected animal, such as a fruit bat or a primate, or even through the practice of eating bush meat or food contaminated with bat faeces; this is known as the spillover event [3,13] – event in which a pathogen from one species moves into another, resulting in a potential outbreak.[14]

After the first human becomes infected, the virus can spread from human to humans via direct contact, such as through broken skin or mucous membranes, with 1) blood, secretions, organs or bodily fluids of a person sick or who has died from EVD; 2) objects contaminated with these fluids; 3) infected fruit bats or primates; and 4) sexual contact with the semen from a man who has recovered from EVD.[3,4] The virus is not spread through the air, water or food[3] and infection through intact skin is unlikely but not entirely excluded.[19] Also, the virus is not transmissible until the infected person starts to develop symptoms (incubation period).[21]

The most infectious bodily fluids are blood, faeces and vomit, however the Ebola virus has also been detected in breast milk, urine and semen and can persist in the last for at least 70 days[5] not being known for how long it can remain, since different men may take different amounts of time for the virus to leave the semen.[3] A study done in Sierra Leone in 2015 showed that the viral load in the semen remained high for as long as nine months after the initial disease.[22]

In early epidemics, the re-use of non-sterile needles was a significant way of transmission in healthcare settings; however this risk is now substantially low and direct contact with an infected person or their bodily fluids is the main way of transmission.[13] In the 2014 West Africa's Ebola Outbreak, direct contact with a person or bodily fluids of a person who has died from EVD has also shown to be a major transmission source; especially since it occurred in countries where traditional funeral ceremonies are practiced.[15] These practices include directly touching or washing the body, followed by distribution of personal property of the deceased.[17] "In the remains of the deceased victims, Ebola lives on" (Haglage, 2015) since all the bodily fluids of the deceased are filled with lethal viral loads able to infect anyone who touches it.[16] WHO mentions that at least 20% of new Ebola infections during the West Africa outbreak occurred during burials of deceased Ebola patients.[17]

Aside from funeral practices, healthcare providers and family members caring for EVD patients are at the highest risk of contracting the disease thus, the healthcare settings are the places where the disease tends to spread more quickly, especially if the healthcare providers are not wearing appropriate personal protective equipment (PPE) (Fig.2).

All personnel caring for an Ebola patient must wear full PPE that completely covers clothing, skin and mucous membranes.[8] According to the CDC (2015), the principals for wearing PPE are as follows:

- Dressing:
  Following the proper order (appendix 1);
  Before entering the patient care area;
  Observed and guided by a trained observer.
- During patient care:
  PPE must remain in place;
  Never be adjusted;
  Frequent and appropriate disinfection of gloved hands with strong chlorine solution, especially after contact with bodily fluids;
  In case of accidental exposure (breach in PPE) to a potentially contaminated fluid, the person must immediately move to the Undressing area to remove PPE and assess the exposure. There should be a facility exposure management plan that needs to be followed.
- Undressing:
  To be performed in a designed area for the purpose;
  In the presence and guidance of a trained observer and an undressing assistant, if needed;
  PPE must be removed slowly and in the correct sequence (appendix 1) in order to reduce the possibility of self-contamination.

Fig. 2 The materials that constitute the PPE, according to the Médecins sans Frontières (MSF) design, and some rules and instructions regarding the PPE.[6]

After infection, development of disease is a complex interplay between virus, host and environment (Goeijenbier *et al*, 2014).[19]

Once tissue invasion occurs, through infected fluid that comes in contact with broken skin or mucosa, the virus tends to invade monocytes, macrophages and dendritic cells that then migrate to the regional lymph nodes and disseminate.[13] The infection of these cells induces an inflammatory state with high levels of proinflammatory cytokines and tissue factor, leading to a pro-coagulant state with impaired endothelial barrier function

that then develops into disseminated intravascular coagulation. All of these events together can lead to a state of severe shock and death.[21]

Even though the mentioned cells are the preferred targets of the virus, it has a wide cell tropism and can infect several cell types[13], such as fibroblasts, hepatocytes, adrenal gland tissue, epithelial and endothelial cells[19]; the infection of these last mentioned cells tends to occur in the final stages of the disease[18], compromising vascular integrity[20].

The replication of the virus inside the infected cells is an extremely efficient and rapid process, leading to a very high viral load very quickly. It is also thought that the death of the infected cells also plays an important role in the disease's symptoms, like the decreased ability of the immune system to respond to the infection due to the death of infected lymphocytes or a decreased production of the clotting factor due to the death of hepatocytes.[19]

From a haematological perspective, leucopenia, lymphopenia and increased liver enzymes are found in the early stages, followed by thrombocytopenia as the disease progresses.[19]

The bleeding complications noted in some of the patients in the more advanced stages of the disease are associated with an overexpression of tissue factor in monocytes and macrophages, leading to an (over)activation of the extrinsic pathway of coagulation followed by coagulopathy and eventually disseminated intravascular coagulation.[19]

The host immune response will dictate the outcome of the disease.[13] An early and well regulated inflammatory responses in association with the prompt release of pro-inflammatory cytokines in asymptomatic patients, is linked with the survival from EVD, suggesting that the innate response plays a crucial role in controlling the infection at its early stages. Fatally-infected patients however are associated with a lack of an early inflammatory response with a massive infection of monocytes and macrophages, the preferred cells of the virus, inducing the release of anti-inflammatory products and probably contributing to the suppression of the inflammatory responses.[18]

Lethal EVD, due to shock, haemorrhage and multi-organ failure, usually takes place between 6 to 16 days after the initial onset of symptoms. However, if the patient recovers, this is accompanied by a development of antibody response[19] and immunity

from the virus for at least 10 years.[24] It's unknown whether this immunity could be life-long or if a new infection with a different species of the EBOV may occur later on.[24]

Survival from EVD depends on good supportive care and the patient's immune response.[24] However the convalescence period is slow and features weight loss and prostration[21].

Upon infection there's an incubation period that ranges from 2 to 21 days, during which time the individual is not infectious;[4] after that, symptoms will start to develop and the victim becomes more and more infectious as the viral load increases.

The early signs and symptoms are non-specific and can mimic other common tropical diseases such as malaria, dengue, typhoid fever and other viral infections, which makes it difficult for an early clinical diagnosis.[2,13] These signs and symptoms are:

- Fever
- Headache
- Fatigue
- Weakness
- Joint and muscle pain
- Sore throat

Progressive gastrointestinal symptoms usually develop within 3 to 5 days from initial symptoms onset: vomiting, diarrhoea, abdominal pain (stomach), nausea, leading to electrolyte imbalance, intravascular volume depletion and shock. Other symptoms as skin rash, hiccups, conjunctival infection, respiratory and neurologic finding may also occur. Hemorrhagic complications appear as a late sign, in less than 20% of patients, alongside with multiple organ failure, and it is usually associated with a bad prognosis. Overall, clinical deterioration may progress in a rapid way and may result in death within 7 to 10 days of symptoms onset.[2,4,7,19] However, there's a 75% chance of survival if the patient lives through the second week of infection.[13]

According to a study done in Sierra Leone between May 25th and June 18th of 2014, the incubation period ranged from 6 to 12 days, the case fatality rate was 74% and the most common clinical features were: fever (89%), headache (80%), weakness (66%), dizziness (60%), diarrhoea (51%), abdominal pain (40%) and vomiting (34%). The

symptoms associated with a fatal outcome were fever, weakness, dizziness and diarrhoea and also, in patients aged above 45 years old (94%) or patients with 10 million or more EBOV copies per millilitre of blood (also 94%).[53] These results are in accordance with another study also done in Sierra Leone between May 29th and December 8th of 2014 by Lado et al, where the most common clinical features were fever or history of fever (83%), intense fatigue or weakness (68%), vomiting or nausea (50%) and diarrhoea (41%).[54]

Rapid and reliable diagnosis of EVD is essential for appropriate and effective patient management, hospital or health center infection prevention and control, and optimization of use of healthcare resources (Martinez *et al*, 2015).[2]

Due to the non-specificity of the initial symptoms and on an human epidemic context, EVD diagnosis is based on the clinical manifestations of the patient and a known contact history with an infected individual in the 21 days prior to the onset of symptoms.[21] If a person has developed symptoms concordant with an EBOV infection and there is reason to believe that EVD should be considered, then the individual must be isolated and public health professionals notified. Blood samples are then collected for testing and confirmation of infection.[1]

Some of the investigations used to confirm an EBOV infection are:[4]

- Antibody-capture enzyme-linked immunosorbent assay (ELISA);
- Antigen-capture detection tests;
- Serum neutralization test;
- Reverse transcriptase polymerase chain reaction (RT-PCR) assay;
- Electron microscopy;
- Virus isolation by cell culture.

These must all be performed in maximum biological containment conditions due to the extreme biohazard risk of the samples.[4]

Prior to 2000, the gold standard for EBOV laboratory detection were antigen detection methods, such as the ELISA, since it has a high sensitivity rate (93%) in the acute stage of the illness. However, as the disease progresses the antigen levels decline and the sensitivity of the test lowers within 1-2 weeks after onset of symptoms. Nowadays,

ELISA has been replaced by RT-PCR (reverse transcription polymerase chain reaction) testing, allowing a more rapid and portable detection.[2]

RT-PCR is a rapid and highly sensitive nucleic acid amplification test and has a very high sensitivity and specificity in detecting the EBOV genome of approximately 100% and 97% respectively.[2]

Through the use of RT-PCR the virus can be detected 48 hours after infection[19], therefore false negative results may occur in the first 2-3 days of the disease since the molecular assay may not be able to detect the genome in such an early stage[2], reason why it is important to take another blood sample 24 to 48 hours after the first one to confirm the result.

During the 2014-2015 West Africa's outbreak the development of rapid diagnostic tests has showed viable options for EBOV diagnosis, with suggestions of sensitivity of 100% and specificity of 90%. Although this is an extremely promising tool it is still not used in daily practice.[2] Some example of this tests are the RealStar Filovirus Screen RT-PCR Kit 1.0, the ReEBOV Antigen Rapid Test Kit and the Xpert Ebola Assay.[55]

	Manufacturer	Detection technique	Viruses detected	Target viral gene	Time to results	Limit of detection	Patient specimen needed
RealStar Filovirus Screen RT-PCR Kit 1.0 (Nov 2014)[3]	Altona Diagnostics GmbH	RT-qPCR	Ebola virus, Sudan virus, Reston virus, Tai Forest virus, Bundibugyo virus, Marburg virus	L	4–6 h (negative), less for a positive	1 plaque-forming unit (about 3400 copies) of Ebola virus or Sudan virus per mL plasma	Plasma collected in EDTA, cell-free bodily fluids, swab washes
ReEBOV Antigen Rapid Test (Feb 2015)[4]	Corgenix	Rapid chromatographic immunoassay	Ebola virus	VP40	15–25 min	$2{\cdot}11 \times 10^8$ RNA copies per mL (extrapolated) or 1×10^4 plaque-forming units per mL (FDA calculated)	Finger-prick (capillary) whole blood, venous whole blood, or plasma collected in EDTA
Xpert Ebola Assay (May 2015)[5]	Cepheid AB	RT-qPCR	Ebola virus	Nucleoprotein and glycoprotein	90 min	82·0 RNA copies per reaction (95% CI 39·7–3193·6)	Venous whole blood collected in EDTA

FDA=Food and Drug Administration.

Table: **Assays for detecting filovirus infections approved for emergency use by the US FDA and WHO**

Fig. 3 Assays for detecting filovirus infections approved for emergency use by the US FDA and WHO (Su *et al*, 2016).

Management of EVD is based on early recognition of infection, accompanied by effective isolation and the provision of the best available symptomatic and supportive care, including rehydration, maintenance of electrolyte balance, nutrition, pain relief and effective blood volume, through blood transfusions, if needed. The main goal of supportive care is to maintain intravascular volume.[2,21]

According to the WHO guidelines, treatment of patients with suspected or confirmed EVD in Ebola Treatment Centres (ETC's) had the following principles:

- Provide basic care such as food and water;
- Patients with fever, especially those with diarrhoea and vomiting, should be encouraged to drink fluids and as much oral rehydration solution (ORS) as can be tolerated;
- Malaria treatment should be provided to all patients with fever, in accordance with national guidelines;
- Medicines to control symptoms can be given orally (fig. 4). Since injections would increase the risk of staff infection can only be given by appropriately trained and assigned staff inside the centre;
- If sufficient oversight is available, oral antibiotics may be given to treat apparent bacterial infections;
- Patient's temperature should be recorded once a shift with a calibrated infrared thermometer.[46]

Symptom	Medicine	Dose
Nausea, vomiting	Ondansetron	Age 4–12 years: 4 mg two times a day Adult: 8 mg two times a day
Diarrhoea	ORS and Zinc	Under 6 months 10 mg daily; Over 6 months 20 mg daily for 10-14
Pain or Fever	Paracetamol	Dose by weight is 15 mg/kg Age 6 months–2 years: 100 mg every 4–6 hours Age 3–5 years: 200 mg every 4–6 hours Age 6–9 years: 300 mg every 4–6 hours Age 10–15 years: 500 mg every 4–6 hours Adult: 1000 mg every 4–6 hours
Epigastric pain	Omeprazole	Once a day before food Age 6 months to 2 years: 10 mg Age 2–12 years: 10 mg Adult: 20 mg
Eye redness, discharge	Tetracycline	Eye ointment for topical application
Agitation, confusion	Diazepam	2 mg to 5 mg per dose, up to 3 doses per day

Fig. 4 Management of common EVD symptoms (WHO, 2015).[46]

The quality of the care provided is strictly related to the outcome of the disease, for example, the difficulties that patient's face in accessing basic medical care in resource poor rural settings reflects a higher case-fatality rate of the disease. Also, failure to

provide full supportive care to the suspected cases[1] may result in substandard care for these, who may later be found to have a treatable disease such as malaria.[2,13]

Specific antiviral medication is still in experimental stages[19] and there are 2 potential vaccines undergoing human safety testing[4], in the meantime and for effective control of an active EVD outbreak, several measures need to be implemented, with an emphasis to case management, surveillance and contact tracing, good and safe laboratory service, safe burials and social mobilization.[4]

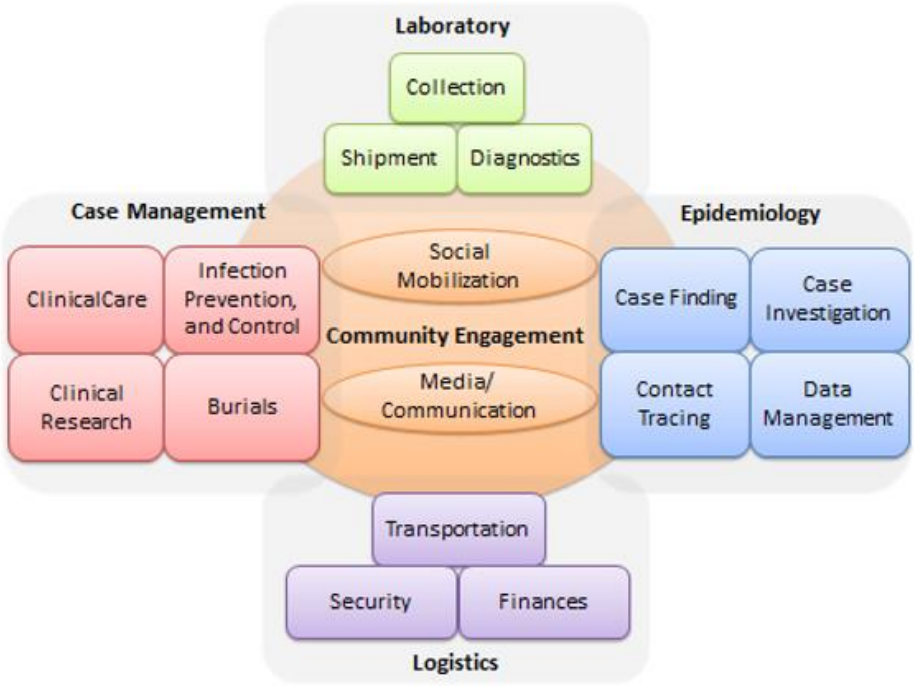

Fig. 5 Structure of the different committees involved in EVD outbreak control activities, according to the WHO, 2015.[26]

Good infection control practices, such as disinfection of contaminated areas and objects (including the patient's home and belongings), also plays a vital role in reducing transmission, plus an attempt on early diagnosis and the use of barriers while performing patient care, like PPE.[13,21]

[1] Definition found in page 12

A study done in Kailahun district, Sierra Leone, found that control can be accomplished by using interventions based on identification and appropriate management of those at risk of developing EVD.[65]

During an outbreak, a combination of Ebola-like symptoms with a high-risk exposure – contact with an EVD patient or body fluids, objects contaminated with body fluids of a person who has died from EVD, attendance to a funeral, contact with an infected animal (fruit bats or primates), contact with the semen of an EVD survivor, visit to a local healthcare or to a known endemic area within the last 21 days – are enough to proceed with isolation and management protocols. It is however essential that there are sufficient patient care capacity and staffing in the specialist facilities.[19,23,65]

Asymptomatic patients with known epidemiological risk factors and persons who may have come in contact with infected patients (called contacts) are considered to be at risk of infection and may need monitoring during the duration of the incubation period.[25] These should be immediately isolated in a room with private bathroom, all attending healthcare personnel must wear PPE and all contaminated materials must be treated as potentially infectious.[13] The recognition of these patients is done by a process called contact tracing[2] (appendix 2) that allows a rapid recognition of symptoms with immediate isolation, testing and provision of care of new cases, thus preventing the future spread of EBOV.[13,25]

Contact tracing is strictly connected to surveillance (case finding) and case investigation measures, since the identification of as EVD case activates a case investigation process where contacts are identified and thus initiating the process of contact tracing. This can only be effective if it's immediately implemented after case finding and efficiently managed.

In order for this to happen, strict definitions must be applied stating what constitutes a "contact", a "suspected EVD case", a "probable EVD case" and a "confirmed EVD case". The WHO (2015) as defined all of the above as shown on the following table:[26]

[2] This is further discussed in section 1.4.2.2. Contact tracing

Denomination	Definition
Suspected EVD case	Any person, alive or dead, suffering or having suffered from a sudden onset of high fever and having 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, diarrhoea, anorexia/loss of appetite, lethargy, stomach pain, aching muscles or joints, difficulty swallowing, breathing difficulties, or hiccup; OR Any person with unexplained bleeding/haemorrhaging; OR Any person with sudden, unexplained death.
Probable EVD case	Any suspected case evaluated by a clinician, OR Any person who died from "suspected" EVD and had an epidemiological link to a confirmed case but was not tested and did not have laboratory confirmation of disease.
Confirmed EVD case	Any suspected or probable cases with a positive laboratory result.
Contact	Any person who has been exposed to a suspected, probable, or confirmed case of EVD in at least one of the following ways (including healthcare workers): ▪ Has slept in the same household as a case; ▪ Has had direct physical contact with the case (alive or dead) during the illness; ▪ Has had direct physical contact with the (deceased) case at a funeral or during burial preparation rituals; ▪ Has touched the blood or body fluids (including urine, faeces, vomit, tears, or sweat) of a case during their illness; ▪ Has touched the clothes or linens of a case; • A baby who has been breastfed by the case.

1.2. Post EVD syndrome[3]

Both short and long term medical problems have been reported in EVD survivors, including mental and physical symptoms. This is referred to as the *Post Ebola virus disease syndrome (PEVDS).*

Definition of an EVD survivor:[51]

- Person with a confirmed positive result on RT-PCR testing for Ebola virus on any body fluid who subsequently recovered; AND/OR
- Person who is IgM and/or IgG positive on serological testing for EVD and has not been vaccinated against Ebola virus.

According to Gulland (2015) "preliminary data show that people who experienced the severe form of the acute infection were more likely to have serious chronic problems" however and for the time being, treatment is still symptomatic and further studies are still needed to fully understand the long-term effects of EBOV infection and the clinical spectrum that occur during PEVDS.[27,29]

Some of the symptoms of PEVDS include: [27,29,51,57,58,61,63]

- *General*: fatigue and anorexia;
- *Musculoskeletal*: chronic joint pain, often severe and debilitating;
- *Ocular*: blurred vision, eye pain, redness, dry eyes, sensitivity to light and, more serious, an inflammatory disease that could lead to blindness if left untreated called uveitis (seen in 50% of survivors in a study done in Port Loko, Sierra Leone, between March 7th, 2015 and April 24th, 2015);
- *Auditory*: hearing loss and tinnitus;
- *Abdominal*: pain from unknown cause;
- *Neurological*: headache, memory impairment, poor concentration, peripheral neuropathy, tremor, sleep disturbances, low mood;
- *Mental health*: post-traumatic stress disorder, fear of death, shame, stigmatization and depression; many survivors were threatened, attacked,

[3] For the purposes of this thesis, the EVD sequelae will be focused on the Zaire species of the virus, even though it has been stated that there are no obvious differences between the species[63]

evicted and excluded by their families and communities because they were seen as still infectious (some of the psychosocial effects can be found below);

Level	Acute effects	Long-term effects
Individual	Fear and/or anxiety (e.g. of infection, death, separation from or loss of loved ones) Shame and/or guilt Frustration, anger or helplessness Stigma and/or isolation Grief and/or loss	Trauma (e.g. from course of infection, witnessing death of others) Grief and/or loss Mental health problems
Community	Fear and/or anxiety Stigma and/or isolation Grief and/or loss Disruption to community and cultural life	Loss of trust (e.g. in health services) Community fracturing Grief and/or loss Loss of support or coping resources
International	Fear and/or anxiety (e.g. of infection) Trauma (e.g. of international aid workers witnessing deaths caused by Ebola virus) Stigma and discrimination Loss of economic investment, business, travel and tourism	Trauma and long-term mental health problems (e.g. of international aid workers witnessing deaths caused by Ebola virus) Stigma and discrimination Loss of economic investment, business, travel and tourism

Fig. 6 Acute and long-term psychosocial effects of an Ebola epidemic at individual, community and international levels (Bortel *et al*, 2016)

- *Sexual health*: erectile dysfunction, testicular pain, dyspareunia, pelvic pain, menorrhagia/metrorrhagia and amenorrhea;
- Relapse due to persistent virus and evaluation of new onset fever, since EVD survivors rapidly clear the virus from the blood as the acute symptoms resolve but the virus may persists for months or years and body sites where the immune system has difficulties reaching (immunological sanctuaries), like the inside of the eyes (aqueous humour), the central nervous system (cerebrospinal fluid), the placenta and amniotic fluid, the mammary gland (breastmilk) and the male gonads (semen).

A good case example of this last point is the case of Pauline, a Scottish nurse who contracted the virus while working on an ETC in December 2014 and was evacuated to the UK where she was transferred to a high level isolation unit, treated and discharged 28 days later. After that she developed symptoms compatible with the PEVDS and since her first admission she already had two more admissions into hospital, one of which

with a case of meningoencephalitis, from virus that remained in the Central Nervous System (appendix 3). More details on the case can be found on the case report done by Michael Jacobs *et al*, 2016.[64]

It is still not clear what are the relations between the pathogenesis and biological events that lead to PEVDS, as is any relation between the severity of the acute disease and the frequency or severity of sequelae (part of what this study plans to identify).[63] According to Vetter *et al* (2016), sequelae could be the result of residual dysfunction from direct viral effects during the acute EVD infection, sustained immune activation, delayed hypersensibility reaction, molecular mimicry, autoimmune disease, or immune complex deposition, individually or in combination.

The fact that the virus may persist in selected body compartments of the survivors, specially the semen, also brings awareness to the possibility of reintroduction of the virus in areas where the virus has already been eliminated.[51] However studies have shown that even if the virus still remains active in other body fluids (aside from semen), its infectivity it's extremely low at this stage.[61,62] "Despite the persistence of Ebola virus in a few body compartments and recrudescence, other than rare reports of suspected sexual transmission, there is no conclusive evidence of virus transmission from convalescence patients" (Vetter *et al*, 2016).

After the high amount of sequelae found in this Ebola's outbreak survivors and it became clear how common this syndrome was, the WHO created a plan to follow-up the survivors for weeks and months following discharge from the ETC. [51]

These follow-up visits would take place: [51]

- 2 weeks after discharge;
- Every month for 6 months following the 2 weeks;
- Every 3 months until completion of one year; and
- Continued follow-up as needed after that.

The first visit would include a general medical history and physical examination, with vital signs recording and nutritional evaluation, plus musculoskeletal, ocular, auditory, abdominal, neurological, mental health and sexual heath evaluations and a consultation with a social worker to address issues related to stigma, economic status and

employment, shelter and food security, dependents, social support, potential substance misuse or dependency and identification of vulnerable individuals. Routine laboratory tests would also be done, including full blood counts, creatinine levels, Ebola RT-PCR testing, plus any other tests that might be needed, such as a malaria rapid diagnostic test.

The following visits would be focused on evaluation the areas relevant to the patient's particular condition, however a complete evaluation, similar to the one done on the first visit, should be done at least every 3 months during the first year. The follow-up visits for the male survivors should also be coordinated with visits made for semen testing.[51]

1.3. EVD outbreaks

The virus was first discovered in 1976 in what is now the Democratic Republic of the Congo, formerly Zaire, and derived its name from the river close to which it was discovered – the Ebola River – since then, several outbreaks have appeared sporadically in Central Africa.[1,2] These outbreaks are usually confined to one country and controlled by the domestic health agencies working with international organizations like the World Health Organization (WHO).[2]

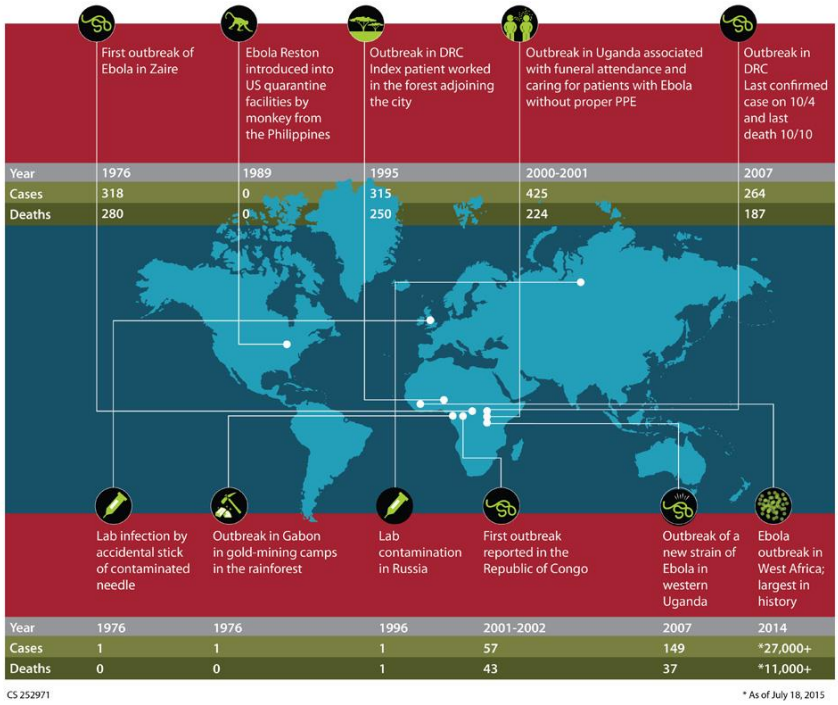

Fig. 7 EVD Outbreaks Chronology (incomplete) as of 18 July 2015, CDC.[10]

To be noted that the map above doesn't show all the known outbreaks that happened between 1976 and 2015. For example, the 1976 South Sudan outbreak, by the Sudan *ebolavirus*, that made 284 notified cases, was omitted from this map. [10]

In total the EBOV has been responsible for 33 notified outbreaks in the African continent.[2] The countries where past EVD outbreaks have occurred are: Democratic Republic of the Congo, Gabon, South Sudan, Ivory Coast, Uganda, Republic of the Congo and South Africa (imported).[9]

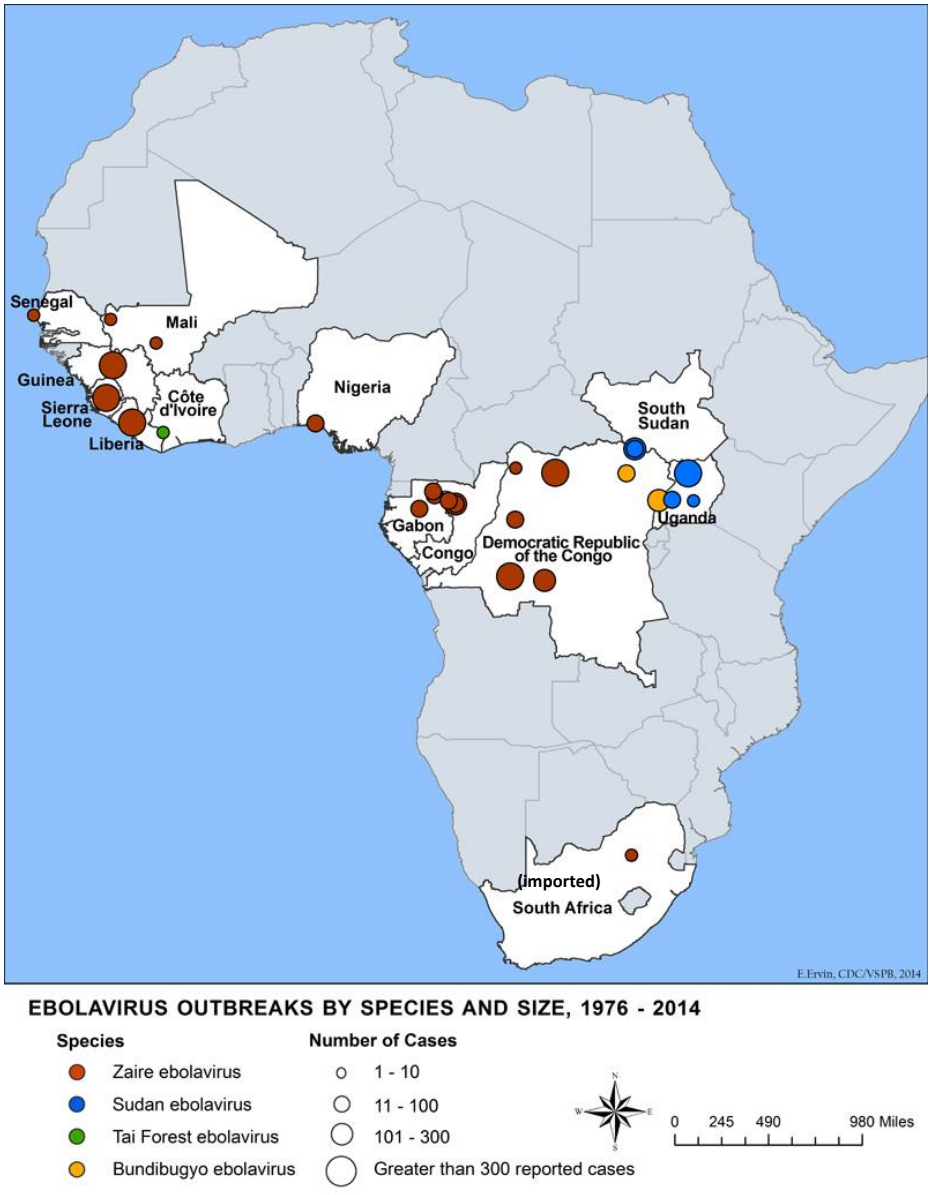

Fig. 8 Ebola virus outbreaks by species and size between 1976 and 2014 (CDC, 2015).[11]

1.4. The 2014 West Africa's EVD outbreak

"The 2014 Ebola outbreak is the largest Ebola outbreak in history and the first Ebola outbreak in West Africa. This outbreak is the first Ebola epidemic the world has ever known" (CDC, 2015).[12]

It started on March 21st 2014, when the Ministry of Health of Guinea notified the WHO of a rapidly evolving outbreak of EVD. The most affected countries of this outbreak were Guinea, Liberia and Sierra Leone and the rapid spread of the disease occurred due to a number of factors including people mobilization and funeral/burial practices.[2,74]

The total number of notified cases in this outbreak was 28 646 cases, causing 11 323 deaths and making over 10 000 survivors.[72]

The first case of EVD in this outbreak (index patient) was retrospectively found to be a 2 year old boy from the village of Meliandou, Guinea, who on the 26th of December, 2013, became ill with fever, melena and vomiting and died 2 days later. It is thought that the boy became infected by ingesting the meat of an infected wild animal, most likely, a fruit bat.[32,42]

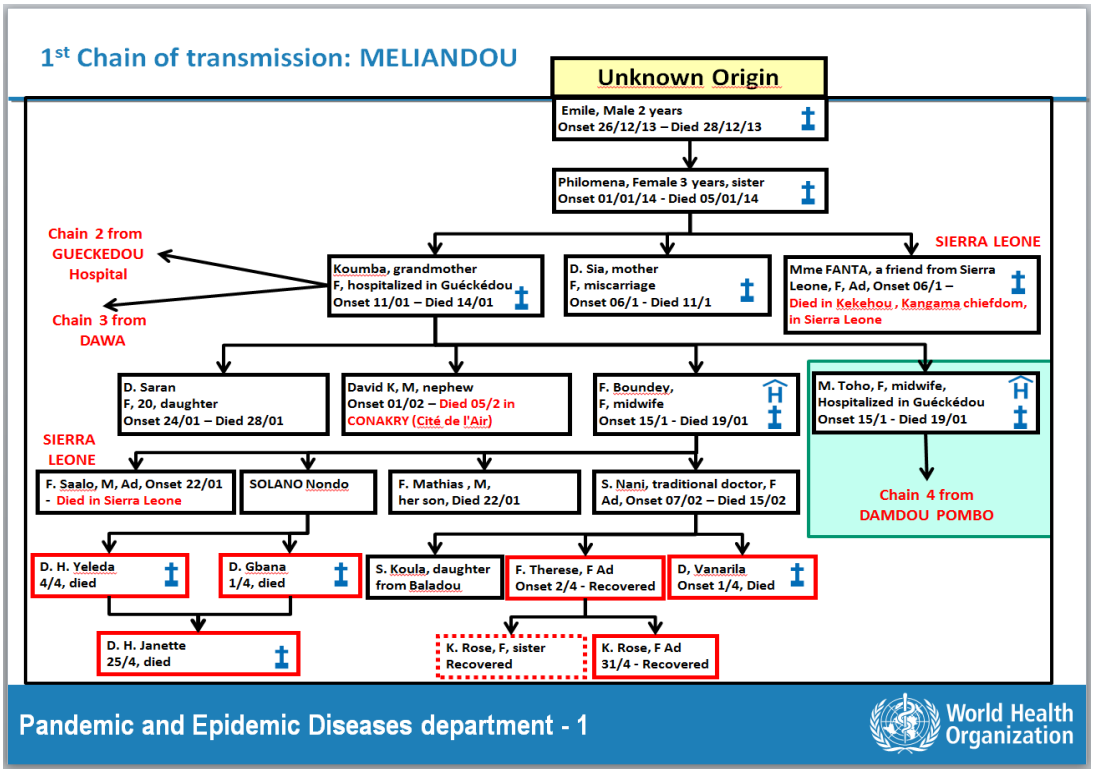

Fig. 9 First chain of transmission (WHO, 2014).[33]

After his death, the virus remained undetected while creating several chains of fatal transmission for over 3 months. It was only in March that the local Guinea health officials, MSF and WHO staff recognised something was happening but were unable to identify it, therefore, the Ministry of Health of Guinea sent blood samples to the institute of Pasteur, in Paris, which identified the causative agent as the *Zaire ebolavirus*, never before seen in this part of the World.[32]

Personal protective equipment and medical teams rapidly started arriving in the country, from both WHO and other Organizations in response to the Outbreak, however, by late March the virus had entered the capital city of Conakry and there were uncontrollable numbers of new cases emerging both in the capital and other parts of the country. Foreign medical teams kept pouring in but the outbreak was out of control.[32]

In April, the number of new cases was increasing by 3.75 per day in Guinea and continued to increase until it reached 19.07 new cases per day in December 2014 (peak of the outbreak).[38]

Liberia reported its first case on the 30th of March 2014 and saw a more attenuated beginning of the outbreak, recording only an increase of 0.15 new cases per day in April 2014 but growing to 47.53 new cases per day by September 2014 (peak).[38,74]

Sierra Leone was the most affected the country of all, beginning the case reporting on the 25th of May 2015 and while in May it was only recording an increase of 0.44 new cases per day it reached and astounding peak of 65.23 new cases per day in November 2014.[38,74]

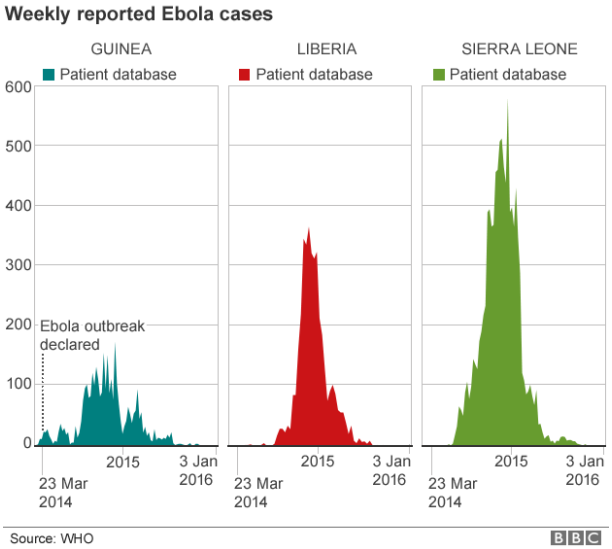

Fig. 10 Weekly reported new cases between 23rd of March 2014 and 3rd of January 2016 (WHO, 2016).[39]

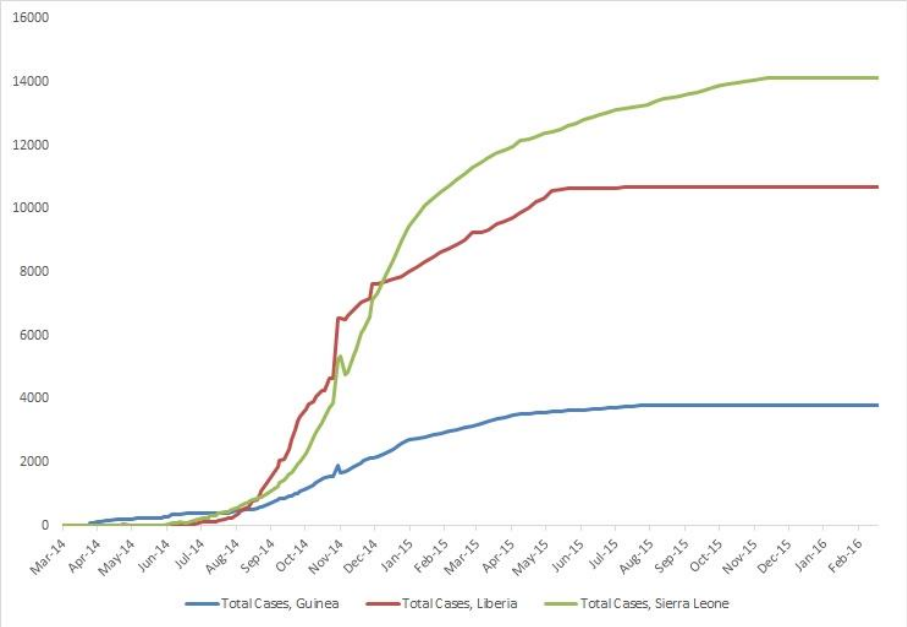

Fig. 11 Total reported suspected, probable and confirmed cases in Guinea, Liberia and Sierra Leone between 25th March 2014 and 14th February 2016 (WHO, 2016).[40]

1.4.1. 2014 West Africa's EVD outbreak major events timeline

- The outbreak was first acknowledged in March, 2014;
- By the end of the month it had already spread to Liberia;
- It entered Sierra Leone in May;
- "In June, the MSF described the Ebola Outbreak as out of control" (BBC, 2016);
- By July, two US workers contracted EBOV and had to be evacuated to the USA;
- Still in July the virus entered Nigeria and two leading doctors on the subject died in Liberia and Sierra Leone;
- The outbreak is declared as an International Public Health Emergency by the WHO on the 8th of August, 2014;
- By the end of August the virus enters Senegal and in October, Mali, via imported cases from Guinea;
- Between September and December 2014, two more US worker, plus a Spaniard and an English workers all are diagnosed with EVD and evacuated to their home countries;

- Germany, Norway, France, Italy Switzerland and the UK all treat patients who contract the virus in West Africa;
- The outbreaks in Nigeria, Senegal and Mali were of small proportions and all had been declared Ebola free by January 2015.[39,41]

A full info graphic with the timeline of the events during this outbreak can be found on Appendix 4.

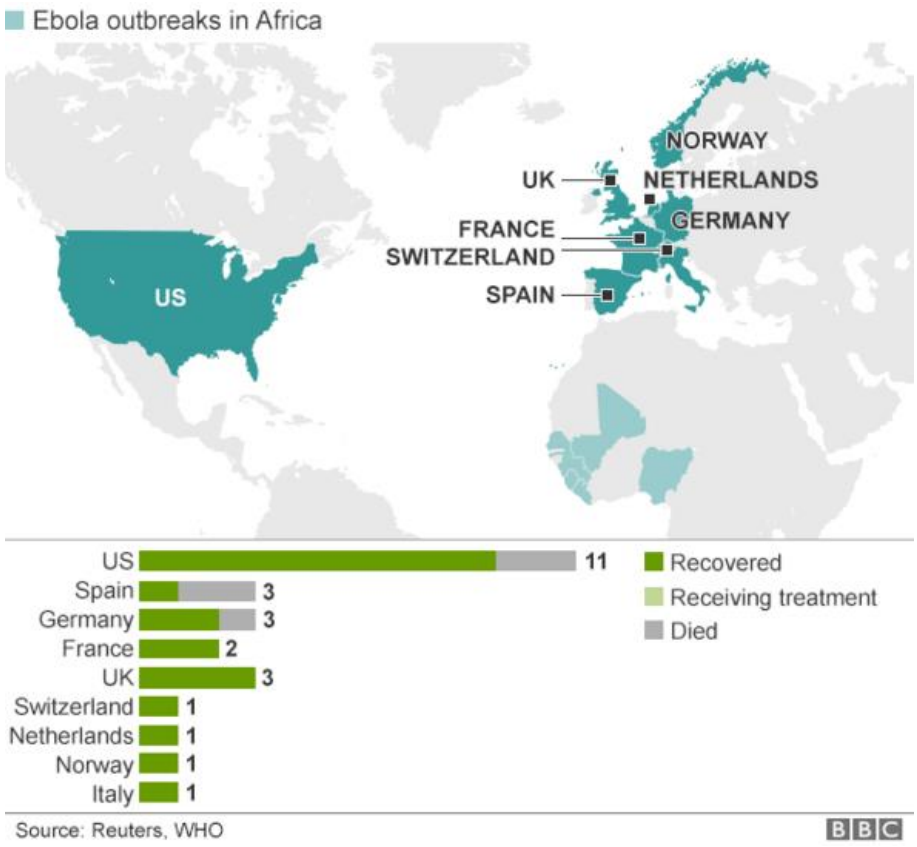

Fig. 12 Ebola outside West Africa (BBC, WHO and Reuters, 2016).[39]

1.4.2 The Ebola Response

After the declaration of the outbreak as an International Public Health Emergency by the WHO in August, several public health interventions needed to be established, including: “early identification of cases; appropriate treatment of people with EVD; physical isolation of cases to reduce further spread; rigorous tracing of contacts; and

burial practices that were safe in terms of EVD-transmission risk and dignified in terms of allowing culturally-appropriate grieving" (WHO, 2015), accompanied by strong social mobilization.[46] With this in mind an "Ebola Response Roadmap" document was created that same month, with the purpose of assisting governments and partners in the revision and resourcing of country-specific operational plans for Ebola Response, and the coordination of international support for their full implementation.[43]

The United Nations Mission for Ebola Emergency Response (UNMEER) was established in September 2014 to complement the Ebola Response Roadmap. It did this by "providing of a common operational platform for enhancing response activities and for addressing the broader consequences of the outbreak" (WHO, 2014).[43] It remained active until July 2015, when the response went back to being led by the WHO in partnership with the local National Ebola Response Centres (NERC).[44,45]

During the Ebola Response and on an international level, the WHO was responsible for the overall health response while the UN was coordinating the overall, multi-sectoral support.[43]

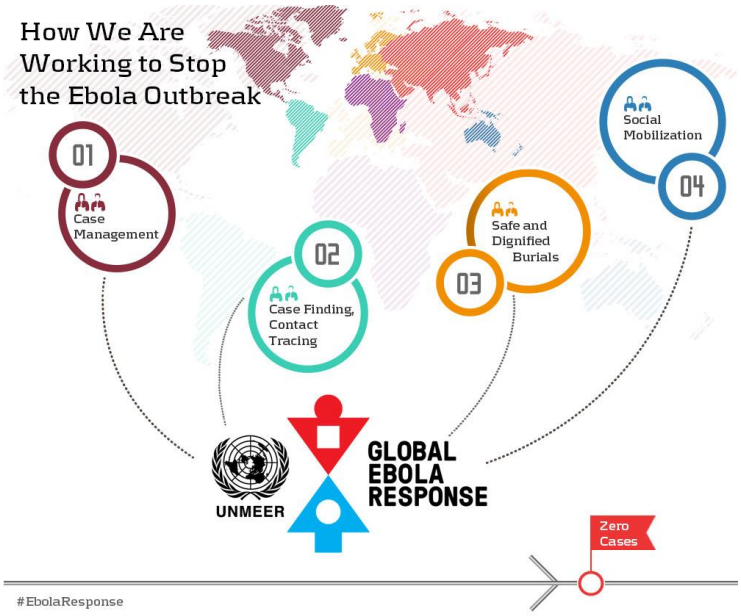

Fig. 13 The four main UNMEER activities (UN, 2016).[44]

Overall, the Ebola Emergency Response defined five objectives:

1) Stop the outbreak;
2) Treat the infected;
3) Ensure essential services;
4) Preserve stability;
5) Prevent further outbreaks.

The response planned to accomplish the objectives through four main activities:

1) Case management;
2) Case finding, lab and contact tracing;
3) Safe and dignified burials;
4) Community engagement and social mobilization.[44]

1.4.2.1. Case management

The WHO priority activities in this area were:

- Ebola treatment centres with full infection prevention & control (IPC) activities;
- Ebola referral/isolation centers (holding centers);
- Referral processes for primary health care facilities;
- Community-based care supported by intensified IPC and appropriate PPE in intense transmission areas.[43]

This was achieved by creating over 60 specialized Ebola Treatment Centres (ETC's), plus over 63 Ebola Community Care Centres (CCC'S) – that later had the name changed to Holding Centers (HC's) – in the three most-affected countries and by having more than 40 organizations and 58 foreign medical teams having been deployed with an estimate of 2 500 international personnel operating on these centers in partnership with ministries of health and thousands of national staff.

In partnership with other NGO's, the WHO was able to provide more than one million sets of PPE and extensive training for health and front-line workers on infection control practices, occupational health and safety, clinical management and safe burials.

This expanded capacity to isolate cases, along with safe and dignified burials and behavioral changes in communities were key factors in controlling the outbreak, even though many cases were still not coming forwards for isolation and treatment leading to Ebola related deaths still occurring in the communities.[45]

ETC's and HC's were the places where most of the care for patients with EVD took place. In these centres, EVD infected people would be isolated and receive basic curative and palliative care, with access to food, hydration, clean clothes and linen.[46] Treatment itself has already been described previously.

The health aid workforce in these centres was formed of both international and local staff that had been trained for this purpose, including training on the protocols of the facility, procedures to be followed if exposure occurs by accident and a temperature check always when entering and leaving the centre (refrain from working when temperature above 38ºC).[46]

Both centres had a similar layout: [46]

Red zone	Green zone
Care of patients suspected or confirmed to have EVD.	All activities that don't pose a risk of EVD transmission:
Clean and disinfect contaminated objects.	- Counselling
Burn waste.	- Rest areas for staff and family
Morgue.	- Supporting services, such as administration, stores, pharmacy, kitchen and laundry for staff's PPE.

The movement of staff inside the centre should always be done from clean to more contaminated areas, including for cleaning purposes (more information on cleaning done inside the centres can be found on Appendix 5).[46]

Entrance to the red zone had to be done through the PPE dressing area and to exit, through the PPE removal area, thus making sure that every member of staff in the red area was wearing FULL PPE.[46]

Patients would enter the red zone through a designated point, different from the staff.[46]

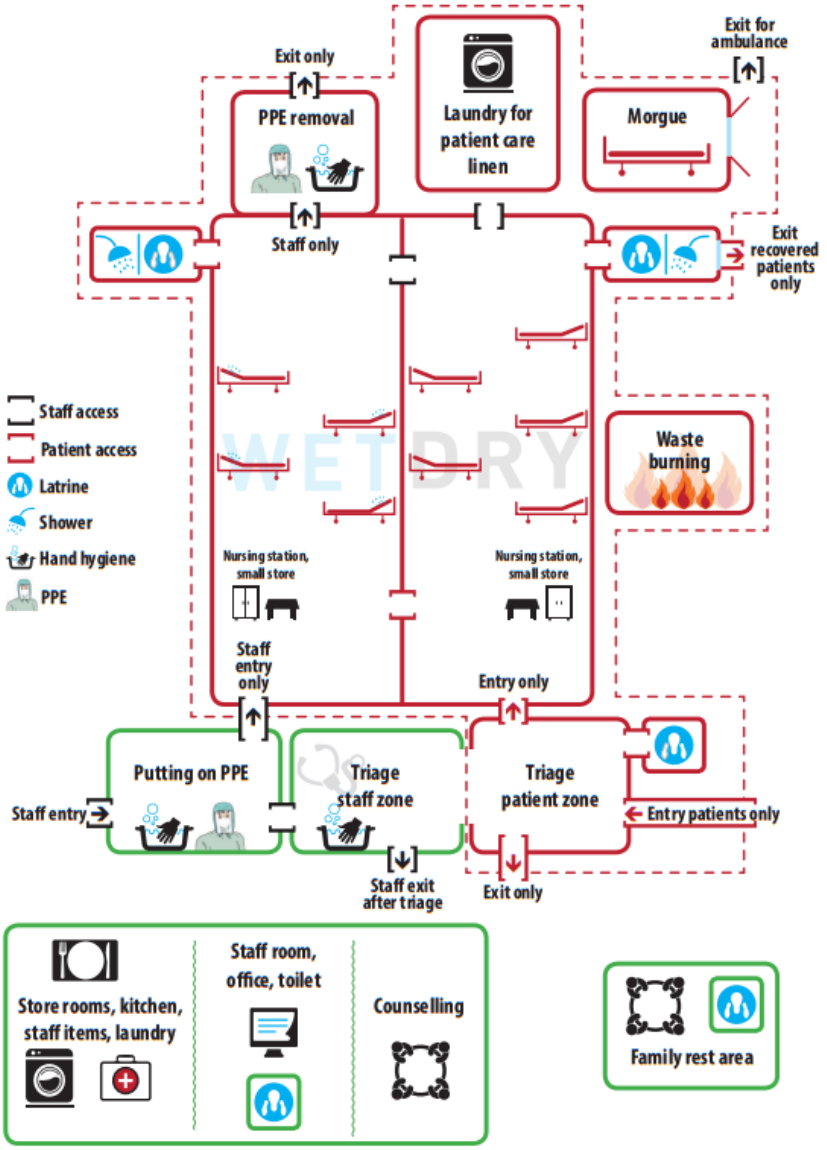

Fig. 14 Centres design and layout (WHO, 2015)[46]

There would be hand washing stations on the entrance and exit of every area inside the centre, both inside the red and green zones and including the entrance/exit of the centre itself. Hand washing should always be done with soap and water or with an alcohol-

based handrub, although many centres didn't have these resources and so, chlorine solutions at a concentration of 0.05% (weak solution), applied for a minimum of 40 to 60 seconds were used and considered appropriate.[46]

Chlorine solutions at a concentration of 0.5% (strong solution) was also available in all centres (mandatory) and was used to clean all the materials that came in contact with suspected, probable or confirmed EVD cases, including PPE, the table in the triage area, the patient's area and belongings (ex: plates, utensils, bedpans and waste buckets), patient's latrines and showers, any spills of body fluids and dead bodies.[46]

Both weak and strong chlorine solutions should be prepared daily in a mixing dedicated area and following an adequate protocol.[46]

All solid infected waste, including PPE, had to be incinerated daily in a burn waste or also called "burning pit" designate for this purpose, which would be located in the red area and down-wind from the centre.[46]

Every patient would enter the centre from the Triage area, where a screening/medical evaluation would be done in the form of an interview and a temperature reading would be taken with an infrared thermometer (appendix 6). If considered to be a suspected or probable case of EVD, the patient would be admitted (appendix 7) and grouped into one of two categories: dry case (fever plus symptoms other than diarrhoea, vomiting or bleeding) or wet case (with diarrhoea, vomiting or bleeding).[46]

Patients found not likely to have EVD would be given items such as home kits or medicines and provided instructions for use and would also be educated on the transmission and prevention of EVD and when to return to the ETC/HC.[46]

After admission and from a patient perspective, the only way out of the centre was either trough the "happy shower" (discharge) or through the morgue.

When recovered, and in order to be eligible to exit the centre (discharge), the patient would have to fulfil certain criteria:

- Patient with fever only and no other symptoms at admission
    - No fever for 72 hours and no other symptoms AND

    - Able to eat and carry out daily routine activities such as walking (taking into account any previous disabilities) and washing themselves independently.
- Patient with fever and other symptoms at admission
    - No fever for 72 hours and other symptoms that may be associated with EVD disappeared for 72 hours AND
    - Able to eat and carry out daily routine activities such as walking (taking into account any previous disabilities) and washing themselves independently.
- If laboratory (PCR) testing is available:
    - A negative test on day following onset of fever and symptoms, or later AND
    - A negative test at least 48 hour after the last positive test.[46]

Leaving the facility was done via the "Happy Shower", which was a joyful event for everyone since it meant the person had survived Ebola. All of the patient's belongings were left behind to be incinerated; the person would enter the "Happy Shower", have a shower with chlorine solution 0.05% and put on clean clothes before exiting the facility.[56]

After discharge, a new stage of the patient's recovery would begin and included dealing with the convalescence stage of the disease, and possible complications that may come with it, reintegration in the community and the fight against the stigma that still surrounds Ebola and Ebola survivors.[56]

On discharge it was also important to advice men to use condoms during sexual intercourse for at least 3 months, after it became known that the virus could remain active in the semen; and alert pregnant women for the fact that miscarriage or foetal death could occur. If so, they should attend an ETC or obstetric clinic equipped with good infection prevention and control (IPC) practices, including full PPE, for delivery of the foetus or any further care needed.[46]

All survivors would also receive education and counselling regarding the possible sequelae and psycho-social consequences during the convalescence period of the

disease[51] and were also advised to link with their local community engagement staff to minimize stigma and discrimination.[46]

If the outcome wasn't a discharge, the management of dead bodies and burials in the centre had to be performed by staff trained in IPC measures and the necessary resources should be present, such as full PPE, body bags, disinfectant and appropriate transportation. Preferably this should be done by a burial team (more information on burial teams on chapter 1.4.2.3.) unless the burial team wasn't able to attend the centre straight away, in which case, and if all the necessary resources and trained staff was present and could safely perform the disinfection of the body and materials, placement of the body inside a body bag and movement it to the mortuary area, this could be performed by trained centre staff, even though the burial itself should and would always be done by the burial team.[46]

Despite the number of centres in operation during the peak of the outbreak, the number of cases was so high that outgrew the capacity of the ETC's and some patients remained at home, placing family members at risk.[46] Not only the shortness of beds led to people staying at home but there were also cases of people who refused to be taken to the ETC due to the stigma surrounding it. Many believed that people were taken there to die since everyone that would go wouldn't return.[59]

In Sierra Leone, Ebola Holding Centres were created at the peak of the Ebola outbreak when ETC's couldn't' provide enough beds for the overwhelming number of new cases seen. Therefore, these units were created as a temporary place to admit and isolate suspected EVD cases until the confirmatory diagnostic testing results came. Those tested positive would then be transferred to the closest ETC and those tested negative would be discharged or referred to other health care facilities, such as the hospital or their local health care centre.[60]

The HC's worked in a similar way to the ETC's, however, according to Zachariah and Harries (2015), they were controversial since they could become very overcrowded, environmental and personal protection measures were limited, and the fear of nosocomial EVD transmission was prevalent. Also, and because the patient's wouldn't be diagnosed or treated for anything else while in the HC's, many other diseases endemic in these areas and whose symptoms mimic the ones from Ebola would go

unnoticed and could lead to serious or even fatal consequences in the centre while waiting for the test results, some examples of these are: severe malaria, typhoid fever and gastroenteritis.

1.4.2.2. Case finding, laboratory and contact tracing

The WHO priority activities in these areas were:

- Case diagnosis: by a WHO-recognized laboratory or by an epidemiologic link to case confirmed by a WHO-recognized laboratory in intense transmission areas;
- Surveillance: contact tracing and monitoring, including new transmission chains.[43]

To achieve these, over 230 experts were sent to 26 mobile laboratories creating an ability to test over 750 samples per day and thus, enabling the rapid confirmation of cases.

Also, over 600 public health experts were deployed to the three most-affected countries during the course of the outbreak response to assist in surveillance, field epidemiology, case finding, contact tracing, information management and epidemiological analysis, which was essential to create and follow chains of transmission and finding new cases from the contacts lists. Contacts were systematically monitored for 21 days and even after the last case had been identified, a long period of surveillance was required to ensure that all chains of transmission were found and there was no re-emergence.[45]

"Contact tracing is the process of identifying, assessing and managing people who have been exposed to a disease to prevent onwards transmission. People who have been exposed to EVD are systematically followed for 21 days (the maximum incubation period for the disease) from the date of the most recent exposure. This process allows for rapid identification of people who become symptomatic. Identifying people at the onset of symptoms and promptly isolating them reduces exposure to other persons, preventing subsequent EVD infections. Additionally, prompt isolation and admission of the symptomatic person to a treatment facility decreases the delay to supportive treatment, which improves the likelihood of survival" (WHO, 2015).[26]

Social mobilization and community engagement efforts are essential to contact tracing since it relies on the active participation and cooperation from the affected communities. These should trust the teams that are conducting case investigations and contact tracing and support the referral of symptomatic contacts to designated isolation and treatment facilities.[26]

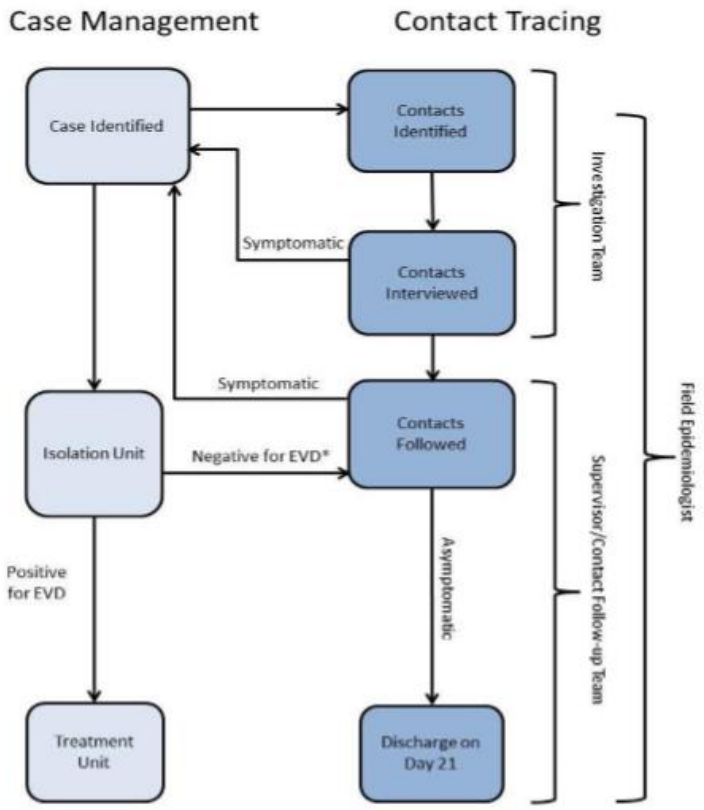

Fig.15 Relationship between case management and contact tracing in the EVD response (WHO, 2015)[26]

After there's been an alert of a possible EVD case, an Investigation team is immediately mobilized to investigate and evaluate the person for EVD symptoms, the type of exposure and any other EVD risk factors. If they meet the criteria for definition of an EVD case, then the Incident Management Framework is activated. Together, the Case management team and the investigation team will interview the EVD case (or its family, in case the person has already died) and identify all potential contacts since the case's onset of symptoms, this might involve several interviews and visiting all the places the

case went while manifesting EVD symptoms. Failure to identify a single contact may lead to ongoing EVD transmission.[26]

All contacts are then personally interviewed and asked about their last interaction with the case, if no risk of exposure is identified, the person will no longer be considered a contact, otherwise, they will be educated about the signs and symptoms of EVD and preventive measures and explained how getting early treatment improves outcome and reduces the risk of infecting others. In case the contact develops symptoms, they are instructed to self isolate and notify the team that will then contact the Field Epidemiologist, who will activate the case management team and the new case will be transported to a transit/isolation unit for further testing. While that happens, new contact identification and contact listing is initiated for this new suspected EVD case (appendix 2).[26]

As a way of following up all contacts, the Contact Follow-up Team should perform daily visits to every contact on the list. Ideally contact teams should be assigned to the same contacts for all 21 days of follow-up. During this visits, the contact will be asked about development of EVD symptoms to him/herself or any other member of the family. If a new suspected EVD case is found, then the cycle restarts as mentioned before.[26]

1.4.2.3. Safe and dignified burials

The WHO priority activities in this area were:

- Supervised burials;
- Trained and PPE-equipped community burial teams.[43]

According to the WHO, a single funeral could be linked to 300 or more Ebola cases.[30] In 2014, in the district of Moyamba, Sierra Leone, a single traditional funeral led to a sharp increase in what was previously a low-incidence district.[48]

This is due to the contact between the mourners and the body and belongings of the deceased when the family and community members perform religious rites that require

directly touching or washing the body and when family members distribute personal property of the diceased.[46, 47]

Therefore a safe and dignified burial protocol[50] and 210 burial teams were created across the three countries in order to bury everyone suspected or confirmed of having died from Ebola in a safe and dignified manner. However, despite this measure, unsafe burials continued to happen throughout the outbreak, especially in Guinea and Sierra Leone, where some communities believed that there were not enough allowance for prayer and spirituality during the burial services.[45]

"Immediate, safe, dignified burials by trained teams with appropriate protective equipment are critical to interrupt transmission and control Ebola during times of active community transmission" (Curran *et al*, 2016).

As an example, in the Sierra Leone's Red Cross, each burial team had around 10 people, which included family liason officers, disinfectant sprayers and drivers. The people working on these teams were people from the community, not medical professionals. Whenever a call came to attend a burial, a swabbing team from the ministry of health would go to the site first, to take fluid samples before the burial team approached, so that the samples could later on be tested and confirmed whether the person died of Ebola or not. However, every death in the community should be considered as an Ebola death and handled as such. When the team arrived at the site, they would first of all, discuss the burial practice with the family, then, put on their PPE, enter the house, place the body of the deceased in a body bag, place the body in a coffin previously arranged with the family, sanitize the family's environment, remove PPE, manage waste and perform hand hygiene, transport the coffin or the body bag to the cemetery, perform the burial at the cemetery following the religious practices desired by the family and return to the headquarters.[49,50]

1.4.2.4. Community engagement and social mobilization

The WHO priority activities in these areas were:

- Full community engagement in contact tracing and risk mitigation and in implementing complementary approaches.[43]

To achieve this it was essential to build a trust between the local communities and frontline workers, through dialogue and education of the community. This included engaging anthropologists with the religious leaders of the community, in order to fight fear and stigma of the disease, to negotiate alternative religious and cultural practices and to encourage the communities to seek treatment. The goal was to create a community engagement model, based on best practice, for the safe and rapid roll out of Ebola treatment and community care centres.[45]

The key messages transmitted by the community teams, local organizations and media were:

- Key facts about severity, transmission and importance of early prevention;
- Information of how to seek treatment for a person with EVD symptoms, how to treat a sick family member at home and for those who have full recovered;
- How to act if there has been a contact with a person alive or dead with EVD;
- Safe burial practices;
- Messaged on what practical steps should be taken to stop Ebola in the community, with focus on effective community mobilization.

These messages were designed to increase the understanding of the EVD and make people less likely to become ill, to enhance the trust inside the community, to promote dialogue and community ownership of the response and to minimize psychological distress. They were selected based on the understanding of their audience and adapted accordingly.[52]

“By promoting community approaches and engaging survivors to work alongside other responders, WHO is helping to minimize stigmatization of communities affected by Ebola” (WHO, 2015).

1.4.2.5. Other measures

To limit national and international spread of the disease, the WHO implemented short-term extraordinary measures were:

- Implementation of specific programmes to ensure continuity of essential and supportive services in containment areas (primary care, food, ...);
- If non-essential movement in and out of a containment area is stopped, ensure that essential movement continues unhindered, such as response providers and essential services;
- To facilitate EVD response, mass gathering should be deferred until intensity of transmission is reduced;
- Prohibit travel of all Ebola cases and contacts (with the exception of medical evacuation);
- Implementations and monitoring of exit screening in international airports, seaports and major land crossings;
- Align practices of all international airlines to the national travel policy.

To ensure essential services and create the foundation for health sector recovery and strengthening of national core capacities for outbreak response the WHO priority activities were to:

- Establish short-term capacity to address critical gaps in essential services, such as health, food, education, security, WASH, through national service providers, NGO's, UN agencies, humanitarian organizations and other partners, based on needs assessment and gaps analysis;
- Develop a medium-term investment plan to strengthen health services that includes syndromic surveillance and laboratory networks to diagnose relevant pathogens;
- Introduce a fast-track training programme for priority health worker gaps, including surveillance.[43]

In September 2015, as the number of cases started decreasing, the goal of the response changed towards achieving and maintaining zero cases with the main objectives at this phase being:

1. To accurately define and rapidly interrupt all remaining chains of Ebola transmission

2. To identify, manage and respond to the consequences of residual Ebola risks.

This last phase of the response (phase 3) aimed to build on the rapid scale-up of treatment beds, safe and dignified burial teams, and behaviour change capacities during phase 1 (August-December 2014) and enhanced capacities for case finding, contact tracing, and community engagement during phase 2 (January-July 2015). It also focused on incorporating new developments in Ebola control, such as vaccines, diagnostics and response operations to survivor counselling and care.[66]

1.4.5. EVD outbreak in Sierra Leone

1.4.5.1. About Sierra Leone

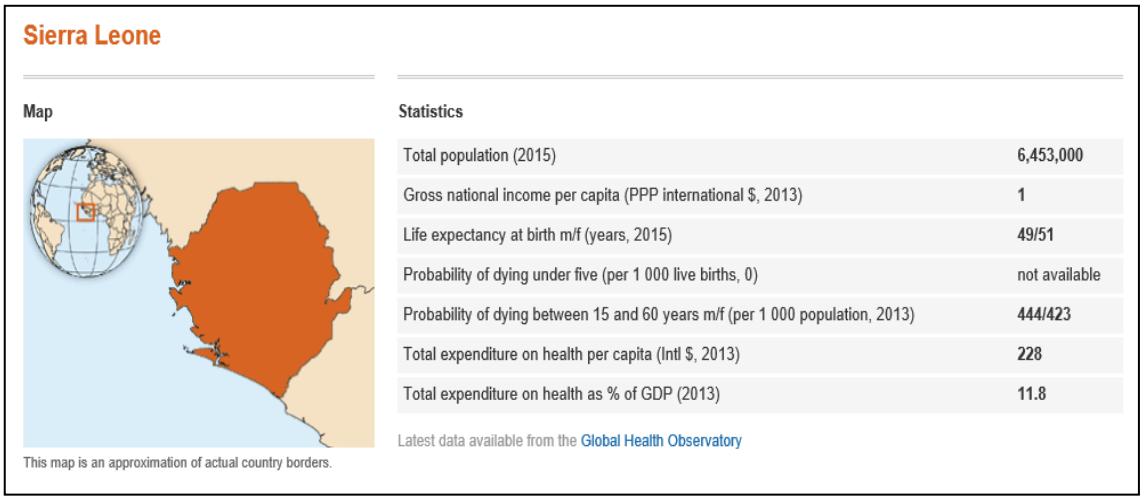

Fig. 16 Statistics on Sierra Leone according to the WHO website, May 28th, 2016.

The Republic of Sierra Leone is a country in the West African coast and part of the 54 countries that make up the whole of the African Continent. It borders Guinea and Liberia and it has a total surface area of 72 000 km^2.[67]

The country is divided by 3 provinces (Eastern, Northern and Southern), one area (Western area), 14 districts and 150 chiefdoms.[70,71]

- 37% of its population resides in urban areas with an expectancy for this number to increase due to the significant rural to urban migration happening;
- 52% of the population is female with an average fertility rate of 5.1 children per woman; 25% of the population constitute women of the reproductive age (15-49); 55% of the population are adolescents and 20% are infants and children under 5 years of age;
- 45% of men and 27% of women are literate;
- 20 languages in total are spoken in the country, being English the official language;
- More information on the Sierra Leone's statistical profile can be found on appendix 8.[67]

Fig. 17 Flag

Fig. 18 Coat of arms

It's one of the poorest countries in the World, ranking180/187 in the United Nations Programme for Development Human Development Index.[73] "The health status of the people of Sierra Leone is still among the worst in the world. Infant and maternal mortality rates remain among the highest in the world. According to the Sierra Leone demographic health survey 2008, life expectancy is 47 years, infant mortality rate is 89 per 1000 live births, under-five mortality rate is 140 per 1000 live births and maternal mortality ratio is 857 per 100 000 births. Fertility rates are high due to low contraceptive use prevalence rate." (ROA, WHO, 2009).

Since the decade of civil war which ended in 2002, that health service delivery in the country has been a challenge due to the damages it created in the health system. It has been substantially dependent on external resources for funding, such as the Asian Development Bank, the Department for International Development (DFID, now known as UKAID), the United Nations Children's Fund, the United Nations Population Fund and the World Bank; and the weakness of the health system continues to undermine standards, availability and accessibility of the services provided.[67]

The governmental body responsible for coordinating health interventions, actions and human workforce in the country is the Ministry of Health and Sanitation (MoHS). It worked with development partners mainly to implement the "National Health Sector Strategic Plan", a 6 year plan created in 2009 to provide a framework for improving the health of the nation by 2015.[67] This plan was mainly focused on fighting HIV, Malaria and Tuberculosis and supporting maternal and child care (Millennium Development Goals), leaving very little external aid to support the overall development of the health system.[69]

The EVD outbreak greatly disrupted the basic essential (non-Ebola) health services in the country, exacerbating the existing weaknesses of the health system and making it even more fragile.[68] If a health system is ill-equipped to deal with a disease outbreak or a catastrophe the affected populations may be extremely vulnerable.[69]

1.4.5.2. The outbreak in Sierra Leone

A young woman who was admitted into a governmental hospital after a miscarriage on the 25th of May, 2014, was the first confirmed Ebola case in Sierra Leone.[30,75]

According to the WHO, the infection entered the country from the neighbouring country Guinea via a traditional healer who lived in Sierra Leone and worked in both Sierra Leone and Guinea. The traditional healer became infected and died. Hundreds of mourners attended the funeral and it's suspected that as many as 365 Ebola deaths are linked to this event.[30]

The outbreak started with this young woman in the Kenema district, quickly spreading to nearby Kailahun district and the Eastern Province adjacent to the epicentre of the outbreak in Guinea. It reached the capital, Freetown, on the 11th of July 2014, where it easily grew into bombastic numbers due to the overcrowded conditions and fluid population movements.[30,70]

Sierra Leone declared a state of emergency on the 6th of August 2014, two days before the International Public Health Emergency being declared by the WHO, and the strategic plan of the UNMEER started its implementation in October 2014, same time by which the Sierra Leone National Ebola Response Centre (NERC) was established to

coordinate this response via the EVD Response pillars: case management, infection prevention and control (IPC) and safe burials, surveillance (and contact tracing), social mobilization and psychosocial support.[70,76,78]

In total, the epidemic in Sierra Leone saw 14 124 notified cases and 3 956 notified deaths. It affected 114 of the 150 chiefdoms, reached its peak in the final quarter of 2014 and started to recede in late November 2014.[70,72]

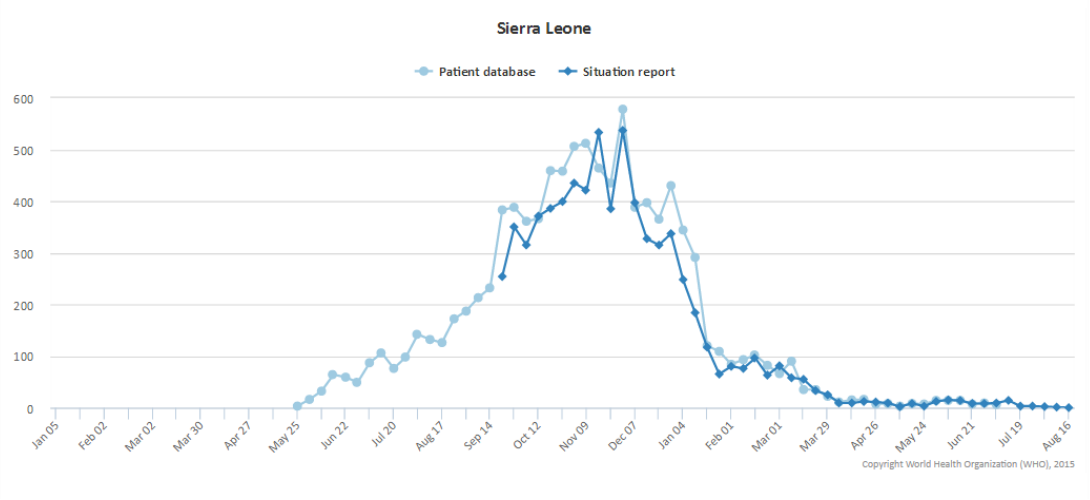

Fig.19 EVD cases count in Sierra Leone during January 2014 and August 2015 (WHO, 2015).[31]

According to the Ministry of Health and Sanitation (MoHS) of Sierra Leone (2014), the challenges that contributed to this massive outbreak included:[75]

- "Inadequate understanding within the communities of the EVD as this is the first major outbreak reported in Sierra Leone.
- Lack of experience among healthcare workers and limited capacities for rapid response.
- High exposure to Ebola virus in the communities through household care and customary burial procedures. This has resulted in high level of community deaths leading to panic and anxiety.
- Denial, mistrust and rejection of proposed public health interventions arising from misinterpretation of the cause of the new disease.

- Fear of the disease by frontline health workers leading to either suboptimal care for patients or substandard implementation of protective measures.
- Close community ties and movement within and across borders has led to difficulties in tracking and following up of contacts for the three countries.
- The magnitude and the geographical extent of the EVD outbreak in Sierra Leone require significant and robust response capacities and structures. This outbreak poses serious challenges in terms of human capacity, financial, operational and logistic requirements and threatens national and international heath."

Fang *et al* (2016), mentions that the multilayer control interventions placed during the last quarter of 2014 were associated with 43% reduction of the population-level transmission risk during intervention phase I and 65% reduction during intervention phase II; these included the establishment and operation of diagnostic and healthcare facilities and the national and regional campaigns to improve case isolation and safe burial (further details about these measures were already mentioned during the Ebola Response section).

1.4.5.3. The outbreak in Nieni Chiefdom, Koinadugu district, Sierra Leone

Koinadugu was the last District of Sierra Leone to be affected by the epidemic; it reached the district by October 2014 even after the local chiefs had imposed measures to prevent the entrance of the virus into the district, such as quarantine, barred travel and created a system of official distribution vans and trucks to help farmers and traders to get their products into the neighbouring markets. The hotspot was in Nieni Chiefdom, being the most affected towns: Kumala, Fankuya and Sumbaria.[77]

The outbreak in this Chiefdom lasted from October 2014 to Mach 2015. During the first 4 months of the outbreak, Kumala's primary school was used as a CCC, named "old Kumala" (aereal picture below). In total, old Kumala admitted 139 patients and saw 70 confirmed cases. In May 2015, a Holding Centre was created with a 20 bed capacity, named "new Kumala".[78] New Kumala never saw a confirmed Ebola case until its closured in October 2015.

The last confirmed EVD case in Nieni Chiefdom (Kumala's CCC) was documented on the 15th of March 2015 adding to a total of 108 cases in this area.[34] The district itself saw a total of 229 cases[36] and was only declared Ebola free on the 29th of May 2015, after having gone 42 days without a recorded case[37].

Fig. 20 Aerial view from old Kumala (Médicos del Mundo, 2015).

1.4.5.4. "End of Ebola Outbreak in Sierra Leone" statement

Delivered by Dr. Anders Nordström, WHO Representative in Sierra Leone on the 7th of November, 2015, Freetown, Sierra Leone:

"Today, 7 November 2015, the World Health Organization declares the end of the Ebola outbreak in Sierra Leone.

Since Sierra Leone recorded the first Ebola case on 24 May 2014, a total number of 8,704 people were infected and 3,589 have died. From those who tragically lost their lives, 221 of them were healthcare workers. We remember them all today.

We are now moving into a new phase of 90 days enhanced surveillance which will run until 5 February 2016. This new phase is critical as our goal is to ensure a resilient zero and that we can detect and respond to any potential Ebola flare ups. This period is about ensuring that we can consolidate the gains of existing systems to manage future risks.

The World Health Organization commends the Government of Sierra Leone and the people of Sierra Leone for the significant achievement of ending this Ebola outbreak.

The World had never faced an Ebola outbreak of this scale and magnitude and the World has neither seen a nation mobilizing its people and resources as Sierra Leone did. The power of the people of Sierra Leone is the reason why we could put an end to this outbreak today.

This power of the people and the foundation now in place needs to be further nurtured and supported in order to build a strong and resilient public health system which stands ready to contain the next outbreak of a disease, Ebola or any other public health threat.

Under the leadership of the Sierra Leonean Government, an effective response was initiated to manage the outbreak. The use of rapid response teams and strong community involvement to identify new cases early and quickly stop any Ebola virus transmission should continue to be the cornerstone of the national response strategy.

WHO will maintain an enhanced staff presence in Sierra Leone as the response transitions from outbreak control, to support enhanced vigilance and to the recovery of essential health services.

The Ebola outbreak has decimated families, the health system, the economy and social structures. All need to recover and heal.

WHO is confident that the Government of Sierra Leone together with its national and international partners will use the foundation already in place; dedicated and trained health workers; systems for alerts and information management; community engagement and care for people – to deal with other priority health problems, child mortality topping the list.

Thank you"[32]

In January 2016 the NERC seized its operations and its responsibilities were taken over by the Ministry of Health and Sanitation, the Ministry of Social Welfare, Gender and Children's Affairs.[76]

2. AIMS

The main goal of this study is to understand if there's any relation between the symptoms during the acute stage of EVD and the sequelae that survivors present moths after recovery.

3. MATERIALS AND METHODS

3.1. Study design and participants

This is a case reports study following the symptoms of 10 EVD survivors on the moment of admission to Kumala's Holding Centre and months after.

The population of the study was selected between the 57 Ebola Case Investigation forms (appendix 9) filled out on time of admission to Kumala's Holding Centre between the dates of 27th of November 2014 and 14th of March 2015.

From the 57 admissions there were 15 confirmed cases, of which 11 survived. Since it was impossible to find information about symptoms months after discharge from one of the survivors, the population of the study made a total of 10 survivors.

3.2. Ethical considerations

Kumala's Holding Centre was created as part of the Ebola Response strategy implemented in Koinadugu district, Sierra Leone. The NGO Médicos del Mundo – Spain – were responsible for the case management and running of this centre.

The official owners of the data collected for this study are the Ministry of Health and Sanitation of Sierra Leone and the Koinadugu District Ebola Response Centre. Authorization has been granted to MdM by the Ministry of Health and Sanitation of Sierra Leone to use the data collected from any MdM projects.

Since I was working at Kumala's HC as part of this NGO, I requested their authorization to pursue this study and present it as my Masters of Tropical Health dissertation, which was granted. It is however to be mentioned that the copyrights of this study will be shared between myself, the Lisbon School of Hygiene and Tropical Medicine and Médicos del Mundo – Spain.

None of the survivors name or village is mentioned in the study; instead they have been numbered at random from 1 to 10. The demographics of the study's population will be mentioned without linking any data to any survivor. The only information linked directly to the survivor's number will be the symptoms they presented on admission to

the HC, 8 months and 10 months after, since these symptoms are the core of the presented study.

3.3. Data collection

As mentioned, the symptoms of the 10 survivors upon admission to Kumala's HC were obtained from the Ebola Case Investigation Forms used during triage (a sample of the form can be found on appendix 9). The symptoms from 8 months after admission were obtained by the psychosocial team working with EVD survivors in Koinadugu district as part of the Médicos del Mundo (MdM) team and granted to me upon request. The 10 months data was collected during an Uveitis program held in Kumala during October 2015, where all the survivors from the district gathered and were screened for uveitis symptoms by an ophthalmologist team and were also seen by a doctor (part of the MdM team) for a medical check-up post EVD; the symptoms were collected from the form used by the MdM doctor during this check-up.

3.4. Data analysis

The data analysis will be descriptive statistics, even though the statistics will have little scientific validity due to the low sample's number. Future studies with larger populations would be needed to confirm or challenge the results obtained in this study.

4. RESULTS

From the 10 survivors, six were females and four males with ages between 5 and 47 years old. Seven had a known contact with a person with EVD (dead or alive) in the 30 days that preceded the symptoms upon admission to the HC. The statistical analysis can be found on the following table.

SEX	
- **Male**	**4 (40%)**
- **Female**	**6 (60%)**
AGE	
Mean	25 years old
AGE GROUPS	
- **0-15**	3 (30%)
- **16-25**	3 (30%)
- **26-35**	2 (20%)
- **36-45**	1 (10%)
- **46-55**	1 (10%)
Known contact with an EVD case in the 30 days prior do admission	
YES	7 (70%)
- **Dead**	6 (86%)
- **Alive**	1 (14%)
NO	3 (30%)

Six out of the ten survivors studied (60%) presented with one or more of the same symptoms months after admission to the centre that they had when the disease was at its acute stage. Four still had headaches ten months after, three maintained weakness, one eye problems, one abdominal pain and another joint pain.

Six survivors (60%) were admitted to KHC presenting severe disease and five survivors (50%) presented severe sequelae up to 10 months after admission, however, from the six that presented severe disease during the acute stage, only three of them also developed severe sequelae.

The following table presents the results regarding the number of symptoms during the three studied stages. When there are five or more symptoms present at that time the number is marked in red, to highlight the possible severity of the disease or sequelae.

	1	2	3	4	5	6	7	8	9	10
Number of symptoms on admission	8	1	8	4	9	10	4	5	5	3
Number of symptoms 8M after	1	4	8	2	No data	1	0	No data	2	6
Number of symptoms 10M after	2	4	6	No data	0	7	6	2	7	10

To be noted that, with the exception of survivor number four, whose data is incomplete, all survivors presented with two or more symptoms 10 months after admission to KHC.

The number of symptoms noted during the three mentioned stages is tabled below.

Symptoms	On admission	8 months after	10 months after
Fever	6 (60%)	1 (12,5%)	
Vomiting	2 (20%)		
Diarrhoea	3 (30%)		
Fatigue		1 (12,5%)	6 (66.7%)
Weakness	5 (50%)	3 (37,5%)	6 (66,7%)
Weight loss	8 (80%)	3 (37,5%)	
Appetite loss		2 (25%)	2 (22,2%)
Abdominal pain	4 (40%)	4 (50%)	
Joint pain	7 (70%)	2 (25%)	4 (44,4%)
Muscle pain	5 (50%)		
Back pain			6 (66,7%)
Chest pain			5 (55,6%)
Headache	5 (50%)	3 (37,5%)	6 (66,7%)
Difficulties breathing	4 (40%)		
Difficulties swallowing	2 (20%)		
Hiccups	-		
Skin rash	1 (10%)		
Eye problems	3 (30%)	4 (50%)	3 (33,3%)
Hearing problems			1 (11,1%)
Sleeping problems			1 (11,1%)

Mood disturbance		2 (22,2%)
Bleeding	2 (20%)	

Unfortunately, I was unable to access the data from two survivors 8 months after the admission to the HC and one other survivor didn't show up to the post-EVD mobile clinic held 10 months later, which is why the percentages for the 8 months after results are calculated out of eight survivors and for 10 months after out of nine survivors instead of 10.

A full list of the 10 survivor's symptoms on admission to the Holding Centre, 8 months later and 10 months later can be found in appendix 10.

5. DISCUSSION

The 2014-2015 West Africa Ebola Outbreak was the largest ever reported in the World. It started in December 2013 and was left unnoticed for 3 months, allowing for the virus to keep spreading uncontrollably and for the outbreak to keep escalating until it was declared an International emergency in August 2014. Despite the large number of cases/deaths recorded, it is to be noted that underreporting was a big issue, especially in the first months of the outbreak, having been predicted by the WHO that the real number of cases during this time was probably 2 to 4 times higher than reported[43].

This was the first ever documented Ebola outbreak outside of Central Africa and it was unmatched in duration and size. Several factors can be contributed to this, such as decades of conflict, increasing population growth, poverty, ethnic and linguistic fragmentation, poor health infrastructures and cultural practices. Due to sociological and economic factors, there's also a large scale movement of populations in the area, both within and between countries, greatly influencing the spread of the disease.[79]

As mentioned, the fact that the outbreak affected extremely poor countries, with severely compromised health systems, lack of knowledge about the virus (and consequent stigma associated with it) and certain kinds of human-to-human contacts, based on religious, behavioural and cultural practices, what led to the rapid spread and increasing fear of the disease. On the other hand, the spread of the virus aggravated the already weakened health system and the fragile social, political and economic conditions of these countries, turning the situation into a vicious cycle where urgent international aid was needed to support the affected countries.

Led and coordinated by the WHO, in partnership with several other UN agencies, national governments and other partners, an international response was established to provide the necessary support to the affected countries. This was done by 1) intensifying response activities, focusing on case management, case finding (surveillance) and contact tracing, safe and dignifies burials, laboratory and social mobilization; and by 2) strengthening national capacities, including the creation of ETC's, CCC's, HC's, burial teams, laboratories and the deployment of large amounts of international staff to work on the field, not only on the centres (since the number of local health care staff was already limited before the outbreak and became even more of

an issue due to the extremely high number of health care workers who were infected and died of the virus), but also engaging with local communities and workers, leading to an increasing understanding about the disease itself, it's transmission and necessary infection control strategies that needed to be continuously implemented in order to reduce transmission, with emphasis on IPC measures and proper use of PPE.

"Achieving real community understanding, ownership and implementation of any complementary approaches, particularly given the deep-rooted fear and stigmatization in the affected areas, required sustained mobilization, engagement and dialogue with community, religious, traditional and other local leaders, woman's and young groups, as well as traditional healers, to build collective trust and confidence in the response efforts and community action" (WHO, 2014).

Community health care workers played a particularly vital role in "delivering messages, addressing stigma and implementing complementary approaches to EVD control" (WHO, 2014), since the fear of this disease led individuals to flee Ebola centres believing they would die there or simple not seek healthcare and revert to traditional healers or family members instead. Being an Ebola healthcare worker was, however, very challenging in such communities since they were awfully stigmatized and rejected by their communities, believing they were acting as reservoirs for the virus. The same would be applicable for EVD survivors.[79]

Fear of stigmatization, alongside burial practices, were probably the main factors that contributed to the magnitude of this outbreak. Burial practices due to the lack of IPC measures during the ceremonies and fear of stigmatization since it influenced disease reporting, pursuing healthcare and overall denial of the disease.

Knowing that the transmission of the virus is done by direct contact and taking into account the behavioural practices of the affected communities, IPC measures were the centre of the intensified control strategies set by the Ebola Response Roadmap, in August 2014, assuming that these would be enough to stop any new transmission within 8 weeks of the index case. It required mobilization of several resources, including medical staffing, material supplies and other essential needs.

Some examples of the complementary control activities implemented, aside from the ones already mentioned, were: 1) all movement of people to and from contaminated/quarantined areas was limited to response providers and essential services; 2) mass gatherings were forbidden during the peak of the outbreak and until the intensity of the virus transmission was reduced, this included closing of schools, bars, restaurants and even of public Christmas celebrations; 3) mandatory temperature checks at various checkpoints including hand washing with weak chlorine solution; 4) implementation of airport, seaport and major land crossings screenings; 5) establishing short-term capacity to address critical gaps in essential services, including health, food, education, protection and WASH, by national, international service providers, NGO's, UN agencies, humanitarian organizations and other partners.

Taking into account that it took the affected countries 3 months to realise there was an Ebola Outbreak devastating their land and the International Health Agencies 5 months after that to declare it a Global Emergency, it is to be questioned if the activities developed at that point were enough to fight the alarming way the virus was spreading at the time. The Ebola Response Roadmap created by the WHO in August 2014 set the goal "to stop Ebola transmission in affected countries within 6-9 months and prevent international spread". This target largely failed, since the end of the outbreak was only declared almost 15 months after. However, it did manage to significantly slow down the transmission significantly by January 2015, five months after the Ebola Response implementation.

From a scientific perspective, the unprecedented high number of cases and subsequent survivors during this outbreak allowed for a lot of research to be done. Nonetheless, it is still not enough and a lot of questions still remain regarding EVD and PEVDS.

Both short and long term complications have been reported on EVD survivors, ranging from physical to psychological and social. In addition, the persistence of EVD in selected body compartments of the survivors poses a great risk of reintroduction of the virus in areas where transmission has previously been eliminated.[51] The PREVAIL III study that began in Liberia in June 2015 and that will last for 5 years, is tracking around 1500 EVD survivors and should bring some insight into the long-term consequences of this infection and also as to how contagious survivors can remain post recovery.

Preliminary findings are already indicating that 68% of survivors hold neurological complications, 60% eye problems and 53% musculoskeletal complications, and that EVD can be found in the semen of male survivors up to 18 months post EVD.[84,85] This is the largest scale survivors study being done and, in comparison with the study presented on this dissertation, neurological (headaches) and musculoskeletal (mainly weakness and back pain) were also the more prevalent sequelae found.

From the data collected in this study, the majority of survivors were females (60%), with an average age of 25 years old (ages ranging from 5 to 47 years) and with 70% of them referring having had contact with a person with known EVD (dead or alive) in the 30 days prior to admission to the HC. The fact that there were more female survivors than male is in accordance with a study done by the WHO Ebola Response Team, mentioned in an article of "The New England Journal of Medicine", in January 2016, stating that there is a higher survival rate amongst female individuals[83].

The most common symptoms recorded on admission (during the active stage of EVD), were **weight loss**, **joint pain** and **fever**; and months after (post EVD) were **headache**, **fatigue**, **weakness** and **back pain** (which could also be related to the sample's professions and not the EVD itself, since most of them were farmers and since musculoskeletal pain is a common complaint in the general population of Sierra Leone).

The psychological complications were not evaluated during this study. However and taking into account what was mentioned before, alongside previous studies done, it is clear that "mental health problems are probably the most prevalent" complications (Marta Lado, as cited by T. Burki, 2016), being depression, anxiety, post-traumatic stress disorder and survivor guilt some of the most common symptoms noted.[84] More studies would still need to be done on this subject.

Gastrointestinal (GI) symptoms weren't very prevalent on these patients upon admission to the HC, which could be related to the fact that GI symptoms tend to appear at a more advanced stage of the acute disease and that the survivors studied could've still been on the initial stage of the disease when admitted. Also, the low frequency of haemorrhagic symptoms it is in accordance with other studies done, alike in a study done by Schieffelin *et al*, published by "The New England Journal of Medicine" in

October 2014, from the 106 Ebola patients that were studied in Sierra Leone, only 1 had haemorrhagic symptoms.[19,53]

Sixty per cent (6 in 10) of survivors presented with one or more of the symptoms they had during the acute stage of the disease months after recovery, being **headache** the most common symptom to persist, followed by **weakness**. However, all survivors presented with one or more symptom months after recovery, regardless of the symptoms existing during the acute stage of the disease (with the exception of one survivor whose data is incomplete).

A study done by Scott *et al*, published by the "Emerging Infectious Diseases" in April 2016, also found that all the survivors studied (44 in total) had between one to five post-Ebola complaints (on average 2), 70% with musculoskeletal pain, 48% with headaches and 14% with ocular problems[86]. This is in keeping with the results found by this study, although it is to be mentioned that the Scott *et al* study was done on survivors only 3 weeks after discharged from an ETC.

The pathogenic and biological events that lead to the development of PEVDS are still unclear and more studies still need to be done on that subject however and taking in consideration a symptomatic approach, **this particular study concludes that the severity of the disease doesn't seem to be associated with the severity of the sequelae** (both defined here by the presence of 5 or more symptoms at a time), since while there were 3 survivors with severe disease that developed severe sequelae, 3 didn't; and while 2 survivors with non-severe disease developed severe sequelae other 2 remained non severe throughout.

However, challenges to this study include the fact that I was only able to analyse a small sample, only 10 survivors, making it difficult to obtain more concrete conclusions. There's also the fact that I didn't have access to symptoms from 2 survivors 8 months after the acute stage of the disease and from 1 survivor 10 months after. And finally, the fact that I was unable to access the records from what happened to the survivors after admission to the Holding Centre or after they had been transferred to the ETC, not allowing me to know how the symptoms developed and making it difficult to compare how the severity of the disease could be related to the PEVD symptoms. Knowledge of the viral load during the acute stage of the disease would also be an important piece of

data information to study to understand if the viral load would have any effect to the symptoms during PEVDS.

With that in mind, it is difficult to conclude from this study if the symptoms during the acute stage of the EVD play an important role in the symptoms seen at PEVDS, more studies overcoming the challenges presented here would be needed.

It would be interesting to continue with studies on EVD survivors, taking into account a larger sample and including more information, such as the psychological effects presented by survivors, all the symptoms that patients presented during the acute stage, from the onset of these until discharge from the ETC, how and when did sequelae started manifesting, the viral load of the patients during the acute stage of the disease and when the symptoms are at its worst and, possibly, making a correlation between all of the above and the remaining of the virus in selected body compartments, such as the eye and the semen.

In conclusion, and in the words of Anders Nordstrom, WHO's representative in Sierra Leone, as cited by Gullard (2015): "we have never had such large number of survivors. This is very new. We have a unique and important responsibility to provide care and support for Ebola survivors trying to restart their normal lives. It is increasingly clear that emerging from an Ebola treatment unit is just the beginning. The countries affected by Ebola also have a long road to recovery".[29]

In Sierra Leone specifically, the President Ernest Bai Koroma, has promised a comprehensive package of free healthcare to all EVD survivors. This, however, is still to be materialized.[84]

Now that the countries have embarked on the recovery journey post Ebolavirus Outbreak, focus needs to be held on other health care problems aside from Ebola, this includes strengthening the current health care systems and restoring essential health services. With such high resource gaps in the health care systems, how can local Governments provide proper care for the survivors? Also, failures in health care systems leads to high mortality from vaccine-preventable and easily-treatable diseases. Therefore, the health care services of the affected countries must now focus back on

immunizations and vaccinations; maternal, newborn, child and adolescent health; and communicable diseases, with an emphasis on Malaria, TB and HIV. [80]

Nonetheless, maintaining IPC measures, laboratory diagnosis, surveillance systems, community engagement, simulations, training, strong workforces and rapid response teams are also important in this recovery stage, since the possibility of re-introduction of the virus in the communities by survivors it's still a harsh reality and the three Ebola-impacted countries remain at high risk of additional small outbreaks.[81]

Since West Africa was declared Ebola-free on the 14th of January of 2016, with all three countries having reached zero cases, there have been small flare-ups in Sierra Leone, Guinea and Liberia and it is expected that more might still happen in the near future.

Prevention and preparedness are essential to protect populations, not only regarding the residual Ebola risk from survivors, but also of any kind of communicable disease epidemic that could lead to an outbreak.[82] The WHO has created tools such as an "Ebola Virus Disease Consolidated Preparedness Checklist" that aims to assist countries in assessing their level of readiness and in identifying concrete actions to be taken to address identified gaps or a "Hospital preparedness for epidemics" providing information on how hospitals and health care facilities can accomplish their role in national and local responses to emergencies.[80]

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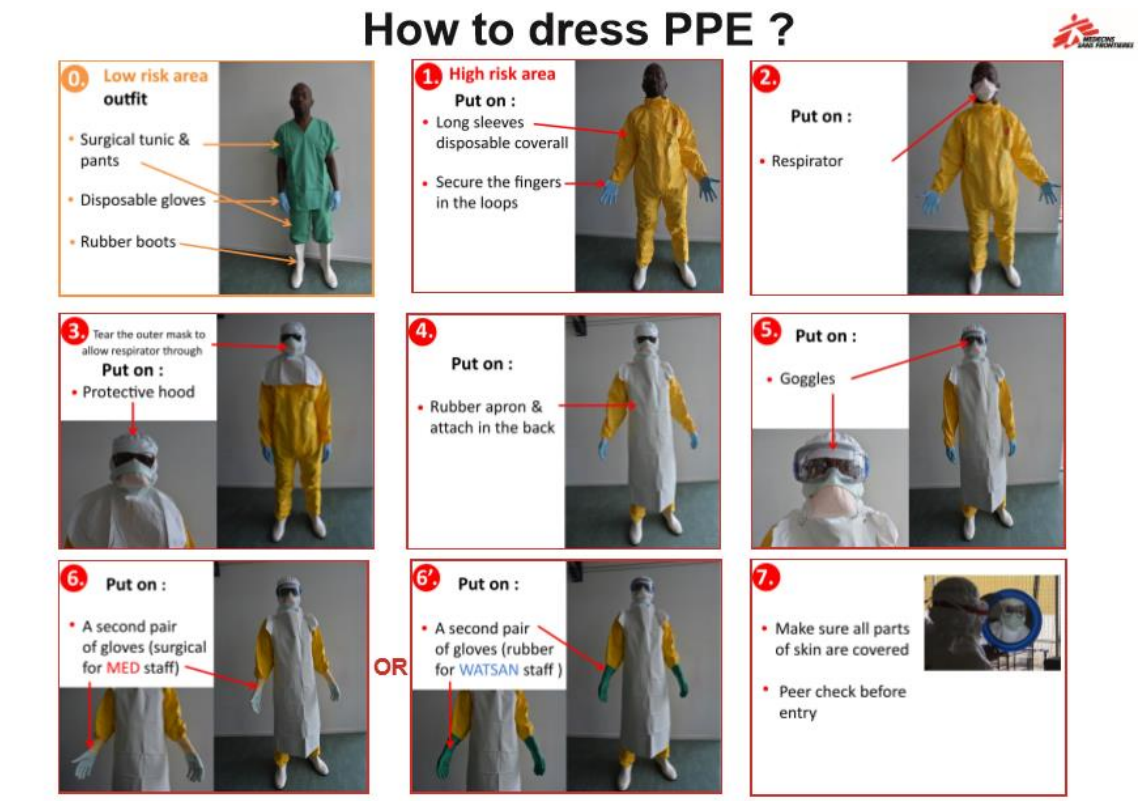
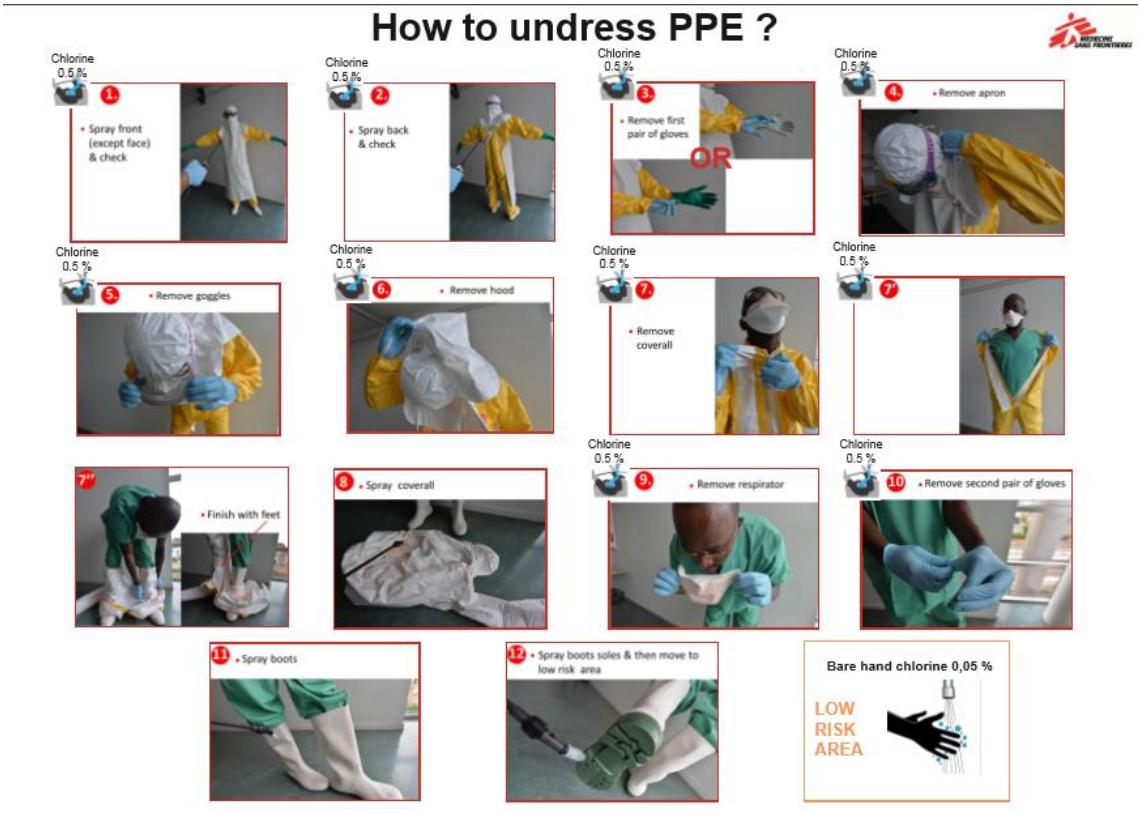
APPENDIXES

Appendix 1: Dressing and Undressing PPE





Appendix 2: Contact tracing

Appendix 3: Case Pauline

Article from MebMD Health News

“Nurse With Ebola, Pauline Cafferkey, Back in Hospital

Peter Russell | February 23, 2016

Scottish nurse Pauline Cafferkey has been transferred to a specialist hospital in London for the third time since contracting Ebola in 2014.

The transfer came hours after the 40-year-old from South Lanarkshire was admitted to the Queen Elizabeth University Hospital in Glasgow for routine monitoring at the Infectious Diseases Unit.

RAF Flight

She was put on an RAF Hercules aircraft which is flying her to London for transfer to the Royal Free Hospital in London.

Ms Cafferkey has been treated in the hospital specialist isolation unit twice during 2015 after contracting Ebola in Sierra Leone in 2014.

The Royal Free has issued a statement, saying: "We can confirm that Pauline Cafferkey is being transferred to the Royal Free Hospital due to a late complication from her previous infection by the Ebola virus. She will now be treated by the hospital's infectious diseases team under nationally agreed guidelines.

"The Ebola virus can only be transmitted by direct contact with the blood or bodily fluids of an infected person while they are symptomatic so the risk to the general public remains low and the NHS has well established and practised infection control procedures in place."

Earlier, NHS Greater Glasgow and Clyde had described Ms Cafferkey's condition as 'stable'.

Ms Cafferkey was first admitted to the high level isolation unit (HLIU) at the Royal Free Hospital in December 2014 after contracting the disease while working as part of a British team at the Kerry Town treatment centre for Ebola patients in Sierra Leone. She was discharged in January this year after making a recovery.

Meningitis

She was re-admitted to the Royal Free HLIU on the 8th October 2015 after the virus triggered a case of viral meningitis.

Bodily tissues can harbour Ebola for some time after a patient appears to have recovered.

At one stage after her re-admission, Ms Cafferkey's condition was described as 'critical', but she was well enough to be discharged from the isolation unit on 12th November last year.

It is not yet known what has prompted her re-admission today.

The Royal Free Hospital in London has an isolation unit and infection control protocols with specially trained staff ready to deal with Ebola cases.

'**A More Complex Disease Than Imagined**'

Dr Derek Gatherer, lecturer in the Division of Biomedical and Life Sciences at Lancaster University, comments in a statement: "It is now becoming clear that Ebola is a far more complex disease than we previously imagined. The very large number of cases in West Africa since the end of 2013, have displayed a wide range of rare but extremely unpleasant consequences for those who survive their first battle with the disease.

"The meningitis that Ms Cafferkey suffered from at the end of last year is one of the most serious complications of all, as it can be life-threatening. She was unlucky enough to be one of only a handful of patients in whom it has been seen."

Dr Gatherer says the other main, but rare, complication seen in patients is eye inflammation which can lead to blindness, while joint aches, headaches and general tiredness can last for months after recovery from Ebola.

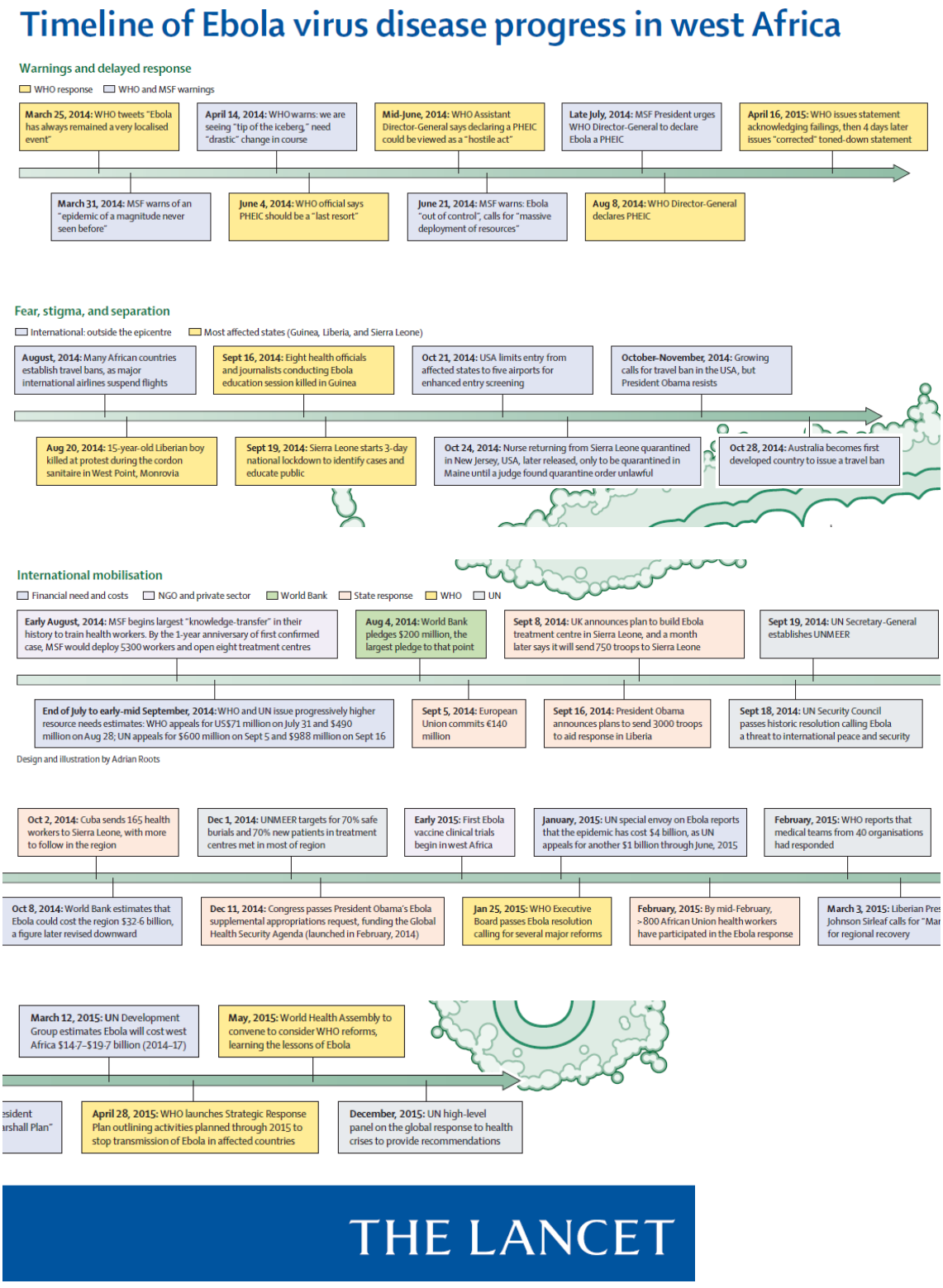
"Up to half of Ebola survivors will have some or several of this milder range of symptoms," says Dr Gatherer. "Although not life-threatening, these can be problematic, especially in societies like west Africa where a large number of people make their living from agricultural labour."

SOURCES:

Royal Free London NHS Foundation Trust. NHS Greater Glasgow and Clyde. Science Media Centre. Reviewed on February 23, 2016”

Available at http://www.medscape.com/viewarticle/859308 accessed 19 May 2016.

Appendix 4: Ebola Info graphic with the outbreak events timeline



Appendix 5: Cleaning and disinfection in the ETC

Cleaning patient areas	
Disinfecting spills of body fluids Do not directly touch the contaminated area	• Cover completely with 0.5% chlorine solution • Let it stand for 10 minutes • Remove with rag or paper towels • Discard rag in plastic bag for infected waste • Wash the area with soap and water, rinse with water and let it dry • Disinfect with 0.5% chlorine solution and let it dry
Cleaning floors and other surfaces not visibly soiled	• Twice a day using disposable towels/rags soaked in soap/detergent solution and then water • Allow surfaces to dry before using
Cleaning latrines and showers	• Clean daily using soapy water • Disinfect with 0.5% chlorine solution
Cleaning contaminated objects	
If not visibly soiled	• Clean with disposable towels/rags soaked in soap and water and then water • If possible soak directly in soap and water, rinse in water, then dry
If visibly soiled	• Follow steps described above for disinfecting spills of body fluids
Washing plates and utensils	• Dispose of leftover food as solid waste • Leave the utensils in 0.5% chlorine solution for a minimum of 10 minutes • Wash them with soap and water • Rinse them with clean water • Let them dry in the sunlight
Bedpan or waste bucket	• Discard contents (see waste management) • Soak and rinse the bedpan with 0.5% chlorine solution
Management of linen	
Bed linen and clothing	• Collect the linen and clothing in leak-proof plastic buckets • Transport them to a designated laundry area • Use washing machine if possible • If not possible, soak them fully in detergent/soap and water, using a stick to stir • Empty the soapy water • Soak the linen and clothing in 0.05% chlorine solution for 30 minutes • Rinse them thoroughly in clean water, using a stick to stir • Dry them on a clothesline
Heavily soiled linen	**DO NOT CLEAN.** Discard and burn (see waste management)
Cleaning and disinfection of re-usable PPE	
Goggles or face shield Heavy duty gloves Boots Heavy duty apron	• Disinfect in 0.5% chlorine solution for 10 minutes • Rinse with clean water • Leave to dry in the sunlight

Source: WHO

Appendix 6: Patient screening in the ETC's triage

EARLY DIAGNOSIS OF EBOLA SUSPECTED CASE WITHOUT LABORATORY TEST AVALIABILITY IN EVD EPIDEMIC AREAS

Name of patient:			
Date of birth:		Age:	
Place:			
Sex:	Male ☐	Female ☐	If female, pregnant: Yes ☐ No ☐

SYMPTOMS

Please tick the symptoms at the time of patient admission:

Dry symptoms	Yes	No	Wet symptoms	Yes	No
Fever	☐	☐	Diarrhoea (watery/bloody)	☐	☐
Weakness/tiredness	☐	☐	Vomiting	☐	☐
Headache	☐	☐	Bleeding from gums, nose	☐	☐
Muscle or joint pain	☐	☐	Blood in vomiting	☐	☐
Stomach pain	☐	☐	Blood in stool	☐	☐
Sore throat	☐	☐	Blood in urine	☐	☐
Redness in both eyes	☐	☐	Miscarriage (pregnancy loss)	☐	☐
Difficulty in breathing	☐	☐			
Hiccups	☐	☐			
Rash	☐	☐			
Measured temperature ___˚C					
Any other symptoms, if present:					

HISTORY OF CONTACT

1) Did you have contact with an Ebola patient (eg: family member, friend or relative suffering from Ebola)? If 'yes':

When (how many days ago): . . . . . .

How/nature of contact (e.g. cared for the patient, washed clothes of patient etc.): . . . . . .

. . . . . .

Where (at home, in a health-care facility): . . . . . .

2) Did you attend a funeral ceremony of someone with EVD or unknown cause of death? If 'yes':

When (how many days ago): . . . . . .

How/nature of contact (e.g. washed the body, touched the body etc.): . . . . . .

. . . . . .

Where (at home, in a health-care facility): . . . . . .

3) In the case of children, was the patient (newborn/child) breastfed by an Ebola patient (EVD case)?

CHECKLIST FOR DECISION MAKING

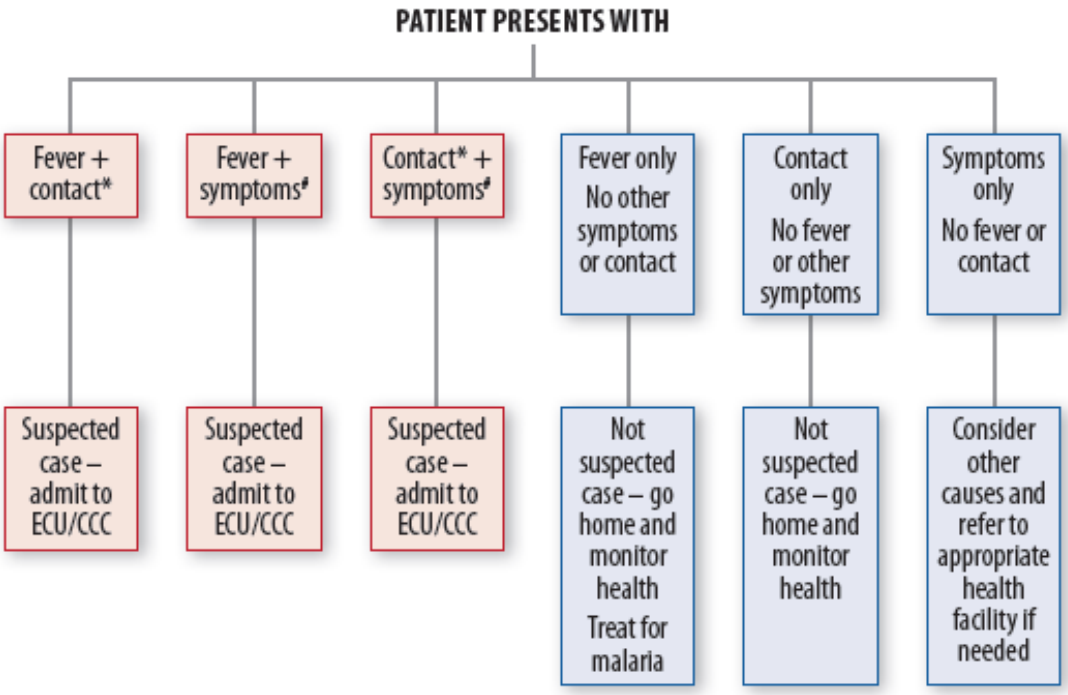
No.	Steps	Status	Remarks
1.	Symptoms presented in the patient noted in indicator table	Yes ☐ No ☐	
	Bleeding signs present	Yes ☐ No ☐	
	Recent history of miscarriage	Yes ☐ No ☐	
	Dry symptoms present	Yes ☐ No ☐	
	Wet symptoms present	Yes ☐ No ☐	
2.	Exposure history present	Yes ☐ No ☐	
3.	Patient provided with malaria treatment	Yes ☐ No ☐	
	Patient provided with antibiotics	Yes ☐ No ☐	
	Patient provided with ORS	Yes ☐ No ☐	
	If provided malaria treatment, decrease in fever noted within 48 hrs of first dose administration	Yes ☐ No ☐	
9.	Patient in Ebola suspected unit	Yes ☐ No ☐	Please indicate: Dry or wet category

ADDITIONAL INFORMATION

If sample taken for lab diagnosis, which sample: blood ☐ swab ☐ Date:	
Record result of test:	
Patient recovered and discharged	Yes ☐ No ☐
Patient died	Yes ☐ No ☐

Source: WHO

Appendix 7: Algorithm for admitting a patient in the ETC



* History of contact with Ebola:

In the past three weeks, has the person:
- Cared for a sick person?
- Washed the clothes of the person who was sick or died?
- Had sexual contact with someone who has since died?
- Touched the body of someone who has died?
- Washed the body of someone who has died?
- Attended the funeral of someone who died from Ebola?
- Touched a sick or dead animal (monkey, fruit bat)?

Symptoms include any three of:

'Dry' symptoms: headaches, extreme tiredness, loss of appetite, nausea, stomach pain, sore throat, breathing difficulties, difficulty swallowing, muscle and joint pain, red eyes, rash, hiccups.

'Wet' symptoms: diarrhoea, vomiting, bleeding (in vomit, stool or urine), foetal loss, unusual or non-traumatic bleeding.

If the patient has a fever lower than 38°C, but describes having had higher fevers before arriving at the ECU/CCC, then that is accepted as meeting the definition of fever.

Source: WHO

Appendix 8: Sierra Leone's statistical profile

Sierra Leone: WHO statistical profile

Basic statistics

Indicators	Statistics	Year
Population (thousands)	6092	2013
Population aged under 15 (%)	42	2013
Population aged over 60 (%)	4	2013
Median age (years)	19	2013
Population living in urban areas (%)	39	2013
Total fertility rate (per woman)	4.7	2013
Number of live births (thousands)	223.3	2013
Number of deaths (thousands)	102.2	2013
Birth registration coverage (%)	78	2010
Cause-of-death registration coverage (%)	...	
Gross national income per capita (PPP int $)	1750	2013
WHO region	African	2013
World Bank income classification	Low	2013

... Data from 2007 onwards not available.

Source:
Country statistics and global health estimates
by WHO and UN partners

For more information visit the Global Health Observatory
(http://www.who.int/gho/en/)

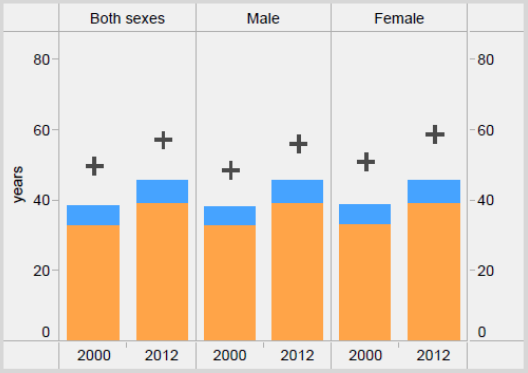
Last updated: January 2015

Life expectancy (years), 2012

		Country	WHO region	World Bank income group
Life expectancy	At birth	46	58	62
	At age 60	13	17	17
Healthy life expectancy	At birth	39	50	53

Life expectancy at birth for both sexes increased by 7 year(s) over the period of 2000-2012; the WHO region average increased by 7 year(s) in the same period.

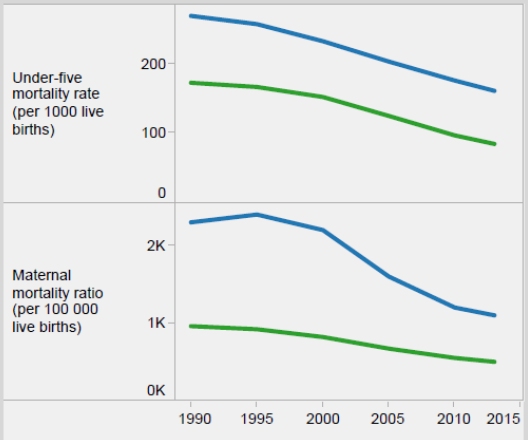
In 2012, healthy expectancy in both sexes was 7 year(s) lower than overall life expectancy at birth. This lost healthy life expetancy represents 7 equivalent year(s) of full health lost through years lived with morbidity and disability.



Millennium Development Goals (MDGs)

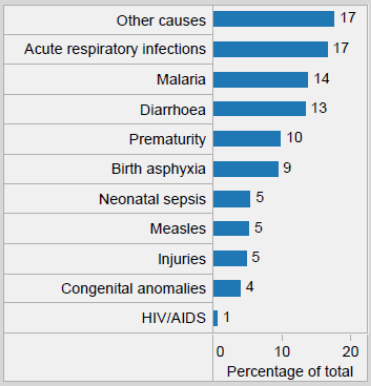
Indicators	Statistics: Baseline*	Statistics: Latest**
Under-five mortality rate (per 1000 live births)	268	161
Maternal mortality ratio (per 100 000 live births)	2300	1100
Deaths due to HIV/AIDS (per 100 000 population)	20.2	54.2
Deaths due to malaria (per 100 000 population)	276.0	101.8
Deaths due to tuberculosis among HIV-negative people (per 100 000 population)	90	43

*1990 for under-five mortality and maternal mortality; 2000 for other indicators
**2012 for deaths due to HIV/AIDS and malaria ; 2013 for other indicators

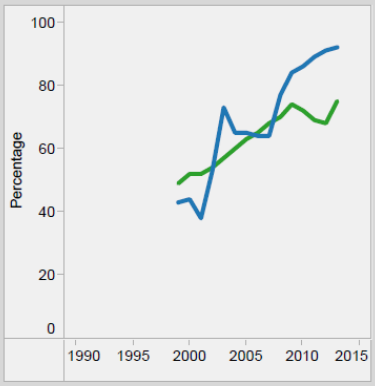


Sierra Leone: WHO statistical profile

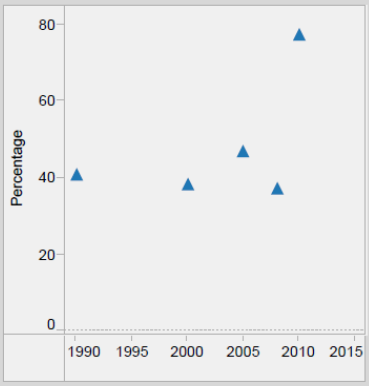
Distribution of causes of deaths in children under-5, 2013



DTP3 immunization among 1-year-olds



Children aged under-5 stunted

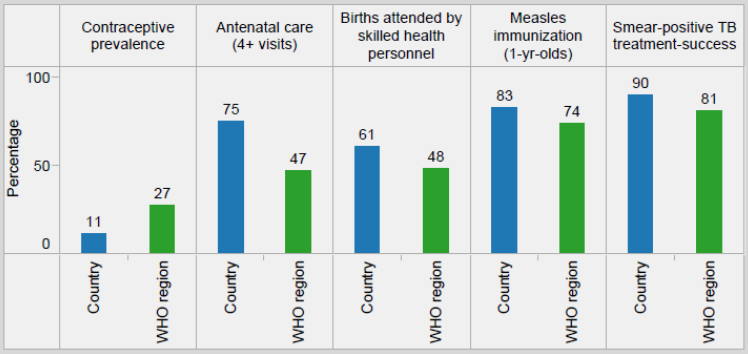


Country
WHO region

Source: Country statistics and global health estimates by WHO and UN partners
For more information visit the Global Health Observatory (http://www.who.int/gho/en//)
Last updated: January 2015

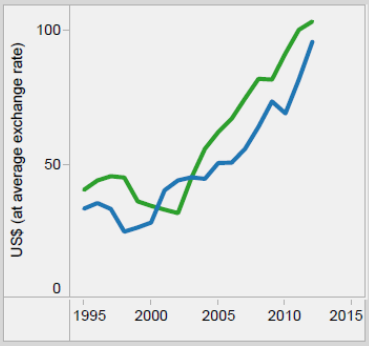
Utilisation of health services*

*Data refer to the latest year available from 2007.

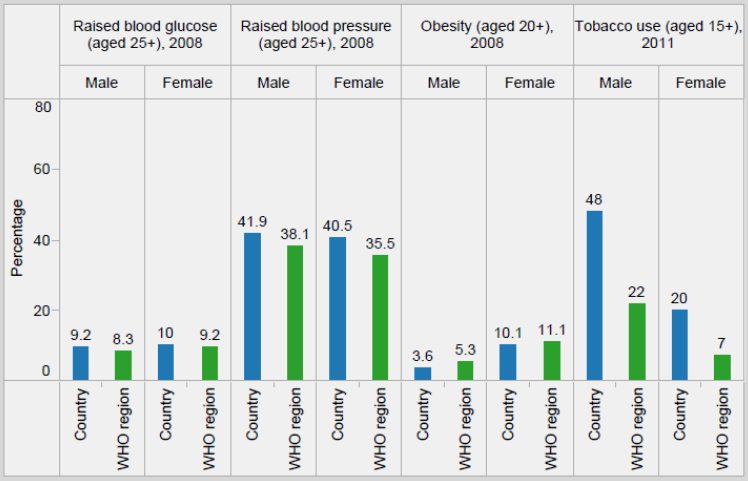


... Data not available or applicable.

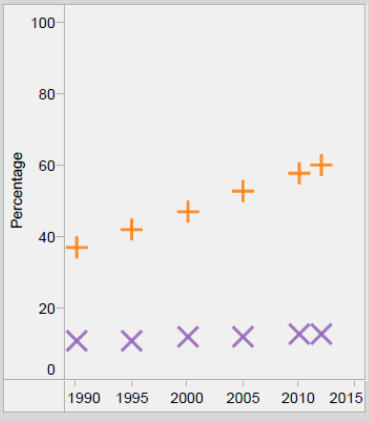
Per capita total expenditure on health



Adult risk factors



Population using improved water and sanitation

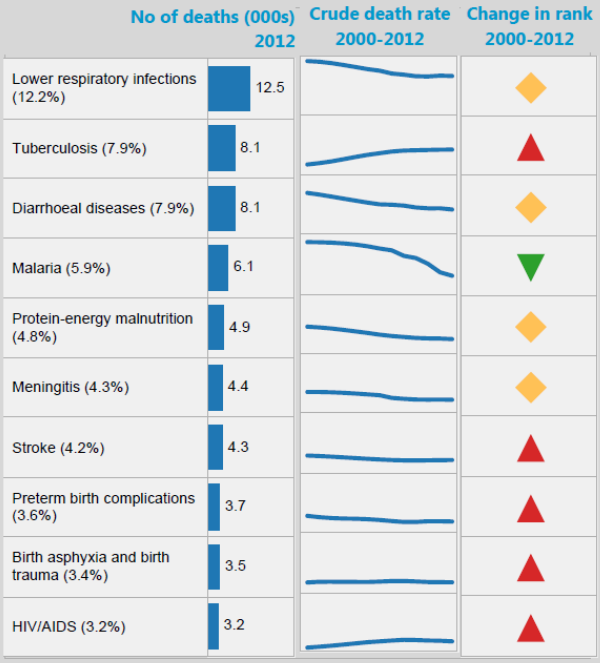


+ Improved drinking-water sources
× Improved sanitation facilities

Sierra Leone: WHO statistical profile

Top 10 causes of death

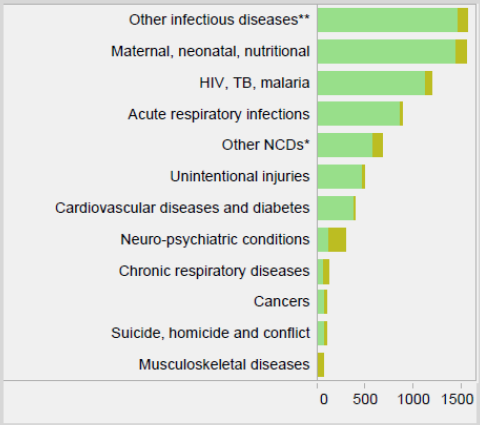
Lower respiratory infections was the leading cause of death, killing 12.5 thousand people in 2012



Burden of disease, 2012

Disability-adjusted life years (DALYs) are the sum of years of life lost due to premature mortality (YLL) and years of healthy life lost due to disability (YLD).

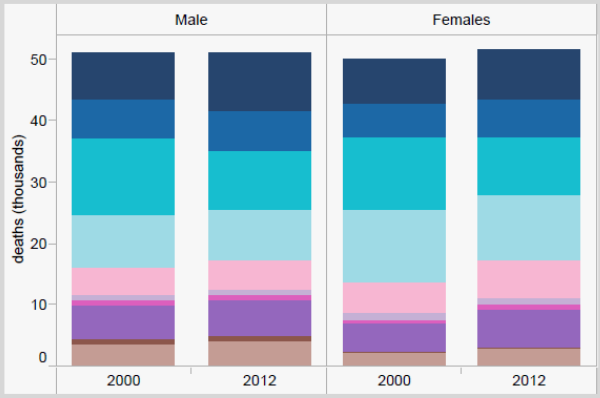
DALYs, YLL and YLD (thousands) by broad cause group



*Other noncommunicable diseases (NCDs) including non-malignant neoplasms; endocrine, blood and immune disorders; sense organ, digestive, genitourinary, and skin diseases; oral conditions; and congenital anomalies.
** Infectious diseases other than acute respiratory diseases, HIV, TB and malaria.

YLL YLD

Deaths by broad cause group



Causes
- HIV, TB, malaria
- Acute respiratory infections
- Other infectious diseases
- Maternal, neonatal, nutritional
- Cardiovascular diseases and diabetes
- Cancers
- Chronic respiratory diseases
- Other NCDs
- Suicide, homicide and conflict
- Unintentional injuries

Probability of dying, 2012

Probability of dying between relevant exact ages, for a person experiencing the 2012 age-specific mortality risks throughout their life.

Before age 15, all causes	Male	55%
	Female	51%
Before age 70, all causes	Male	91%
	Female	89%
Between ages 15 and 49, from maternal causes	Female	58%
Between ages 30 and 70, from 4 major noncommunicable diseases (NCDs)~	Both sexes	27%

~Cancers, cardiovascular diseases, chronic respiratory diseases and diabetes

Source: Country statistics and global health estimates by WHO and UN partners
For more information visit the Global Health Observatory (http://who.int/gho/mortality_burden_disease/en/)
Last updated: January 2015

Appendix 9: Ebola Case Investigation form used at Kumala's Holding Centre

EBOLA CASE INVESTIGATION FORM – Sierra Leone

Date of Case Report: ☐☐/☐☐/☐☐☐☐ Outbreak Case ID:

☐ Patient is a followed contact: ***Convert to CASE in VHF***

Complete at end of interview: ☐ suspect ☐ probable ☐ unk

Patient's Last Name: _____ **First Name:** _____

Age: _____ Unit: ☐ Years ☐ Months Gender: ☐ Male ☐ Female

Patient Status at Time of This Report: ☐ Alive ☐ Dead ***If dead,*** Date of Death:

Permanent Residence:

Head of Household: _____ Village/Town: _____

District: _____ Chiefdom: _____ Mobile phone #: _____

Patient's Occupation:

☐ Healthcare worker (includes anyone involved with the patient: nurse, ambulance driver, hospital cleaner, etc.)

Position: _____ Healthcare facility: _____.

☐ Other; please specify occupation: _____.

Location Where Patient Became Ill:

Village/Town: _____ District: _____ Chiefdom: _____

Date Patient First Became Sick: ☐☐/☐☐/☐☐☐☐

Read each one aloud and mark an answer for every symptom occurred during this illness (not only right now):

Fever	☐ Yes	☐ No	☐ Unk	Headache	☐ Yes	☐ No	☐ Unk
Vomiting/nausea	☐ Yes	☐ No	☐ Unk	Difficulty breathing	☐ Yes	☐ No	☐ Unk
Diarrhea	☐ Yes	☐ No	☐ Unk	Difficulty swallowing	☐ Yes	☐ No	☐ Unk
Conjunctivitis (red eyes)	☐ Yes	☐ No	☐ Unk	Skin rash	☐ Yes	☐ No	☐ Unk
Intense fatigue/weakness	☐ Yes	☐ No	☐ Unk	Hiccups	☐ Yes	☐ No	☐ Unk
Anorexia/loss of appetite	☐ Yes	☐ No	☐ Unk	Unexplained bleeding	☐ Yes	☐ No	☐ Unk
Abdominal pain	☐ Yes	☐ No	☐ Unk	If yes, please specify:			
Muscle pain	☐ Yes	☐ No	☐ Unk	Other symptoms:	☐ Yes	☐ No	☐ Unk
Joint pain	☐ Yes	☐ No	☐ Unk	If yes, please specify:			

At the time of this report, is the patient hospitalized or being admitted to the hospital? ☐ Yes ☐ No ☐ Unk

If yes, Date of Hospital Admission ☐☐/☐☐/☐☐☐☐

Hospital Name: _____ District: _____

Is the patient now, or will he/she soon be, in an Ebola treatment unit? ☐ Yes ☐ No ☐ Unk

If yes, date of admission (or future admission to the ETU (isolation): ☐☐/☐☐/☐☐☐☐

Was the patient hospitalized or visited a clinic previously for this illness (this includes any type of care: pharmacist, traditional healer, etc.)? ☐ Yes ☐ No ☐ Unk

If yes, Dates of Hospitalization: ☐☐/☐☐/☐☐☐☐

Hospital Name: _____ District: _____

Uniprint-F_SA

IN THE PAST ONE (1) MONTH PRIOR TO SYMPTOM ONSET: Outbreak Case ID:

1. Did the patient have contact with a suspected or confirmed Ebola case in the one month before becoming ill?

☐ Yes ☐ No ☐ Unk

If yes, please complete one line of information for each sick source case:

Name of Source Case	Relation to Patient	Date of Last Contact (DD, MM, YYYY)	Village/Town	District	Was the person dead or alive?
		__/__/__			☐ Alive ☐ Dead Date of Death: __/__/__ (DD,MM,YYYY)
		__/__/__			☐ Alive ☐ Dead Date of Death: __/__/__ (DD,MM,YYYY)

2. Did the patient attend a funeral in the one month before becoming ill? ☐ Yes ☐ No ☐ Unk

If yes, Name of deceased person	Relation to Patient	Date of Funeral (DD, MM, YYYY)	Village/Town	District	Did the patient participate? (carry or touch the body)?
		__/__/__			☐ Yes ☐ No

3. Did the patient travel outside their hometown or village/town before becoming ill? ☐ Yes ☐ No ☐ Unk

If yes, Village: _____ Chiefdom: _____

District: _____ Date(s): D D / M M / Y Y Y Y - D D / M M / Y Y Y Y

Case Report Form Completed by:

Name: _____ Phone: _____ E-mail: _____

Position: _____ District: _____ Health Facility: _____

Information provided by:

☐ Patient ☐ Proxy *If proxy,* Name: _____ Relation to patient: _____

Patient Outcome Information:

Please fill out this section at the time of patient recovery and discharge from the hospital OR patient death.

Date Outcome Information Completed: D D / M M / Y Y Y Y

Final Status of the Patient: ☐ Alive/Recovered ☐ Dead

If the patient has recovered and been discharged from the hospital:

Hospital discharged from: _____ District: _____

Date of discharge from the hospital: D D / M M / Y Y Y Y

If the patient is dead:

Date of Death: D D / M M / Y Y Y Y

Place of Death: ☐ Community ☐ Hospital District: _____

Date of Funeral/Burial: D D / M M / Y Y Y Y

Funeral conducted by: ☐Family/community ☐ Outbreak burial team

Place of Funeral/Burial: Village: _____ Chiefdom: _____ District: _____

Appendix 10: Table of results

Symptoms of the 10 survivors on admission to the HC, 8 and 10 months after

	SURVIVOR 1			SURVIVOR 2		
SYMPTOM	ON ADMISSION	8M AFTER	10M AFTER	ON ADMISSION	8M AFTER	10M AFTER
FEVER	X					
VOMITING	X					
DIARRHOEA						
FATIQUE						
WEAKNESS	X				X	
WEIGHT LOSS	X				X	
APPETITE LOSS					X	X
ADBOMINAL PAIN	X					X
JOINT PAIN	X					
MUSCLE PAIN	X					
BACK PAIN						X
CHEST PAIN			X			
HEADACHE	X	X	X	X		
DIF. BREATHING						
DIF. SWALLOWING						
HICCUPS						
SKIN RASH						
EYE PROBLEMS					X	X
HEARING PROBLEMS						
SLEEPING PROBLEMS						
MOOD DISTURBANCE						
BLEEDING						

	SURVIVOR 3			SURVIVOR 4		
SYMPTOM	ON ADMISSION	8M AFTER	10M AFTER	ON ADMISSION	8M AFTER	10M AFTER
FEVER		X		X		
VOMITING						
DIARRHOEA						
FATIQUE			X			NO DATA
WEAKNESS	X	X	X			
WEIGHT LOSS	X	X		X		
APPETITE LOSS		X				
ADBOMINAL PAIN	X	X			X	

JOINT PAIN	X	X		X		
MUSCLE PAIN	X					
BACK PAIN			X			
CHEST PAIN			X			
HEADACHE		X	X			
DIF. BREATHING	X			X		
DIF. SWALLOWING	X					
HICCUPS						
SKIN RASH						
EYE PROBLEMS	X	X	X		X	
HEARING PROBLEMS						
SLEEPING PROBLEMS						
MOOD DISTURBANCE						
BLEEDING						

	SURVIVOR 5			SURVIVOR 6		
SYMPTOM	ON ADMISSION	8M AFTER	10M AFTER	ON ADMISSION	8M AFTER	10M AFTER
FEVER	X			X		
VOMITING						
DIARRHOEA	X			X		
FATIQUE						X
WEAKNESS	X			X		X
WEIGHT LOSS	X			X		
APPETITE LOSS						
ADBOMINAL PAIN	X					
JOINT PAIN	X			X		X
MUSCLE PAIN	X			X		
BACK PAIN		NO DATA	NO SYMPTOMS			X
CHEST PAIN						
HEADACHE				X		X
DIF. BREATHING	X			X		
DIF. SWALLOWING				X		
HICCUPS						
SKIN RASH						
EYE PROBLEMS	X				X	X
HEARING PROBLEMS						
SLEEPING PROBLEMS						
MOOD DISTURBANCE						X
BLEEDING				X		

	SURVIVOR 7			SURVIVOR 8		
SYMPTOM	ON ADMISSION	8M AFTER	10M AFTER	ON ADMISSION	8M AFTER	10M AFTER
FEVER	X			X		
VOMITING						
DIARRHOEA						
FATIQUE			X			X
WEAKNESS			X			X
WEIGHT LOSS	X			X		
APPETITE LOSS						
ADBOMINAL PAIN						
JOINT PAIN			X	X		
MUSCLE PAIN				X		
BACK PAIN		NO SYMPTOMS	X		NO DATA	
CHEST PAIN			X			
HEADACHE	X		X			
DIF. BREATHING						
DIF. SWALLOWING						
HICCUPS						
SKIN RASH				X		
EYE PROBLEMS	X					
HEARING PROBLEMS						
SLEEPING PROBLEMS						
MOOD DISTURBANCE						
BLEEDING						

	SURVIVOR 9			SURVIVOR 10		
SYMPTOM	ON ADMISSION	8M AFTER	10M AFTER	ON ADMISSION	8M AFTER	10M AFTER
FEVER						
VOMITING	X					
DIARRHOEA	X					
FATIQUE			X		X	X
WEAKNESS		X	X	X	X	X
WEIGHT LOSS	X				X	
APPETITE LOSS						X
ADBOMINAL PAIN	X	X	X		X	
JOINT PAIN			X	X	X	X
MUSCLE PAIN						
BACK PAIN			X			X
CHEST PAIN			X			X
HEADACHE			X	X	X	X

DIF. BREATHING						
DIF. SWALLOWING						
HICCUPS						
SKIN RASH						
EYE PROBLEMS						
HEARING PROBLEMS						X
SLEEPING PROBLEMS						X
MOOD DISTURBANCE						X
BLEEDING	X					