

MSF - OCB SUPPORTED RESEARCH ON EBOLA

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Abbreviations

ETC Ebola Treatment Centre
EVD Ebola Virus Disease
GIS Geographical Information System
MoH Ministry of Health
MSF Medecins Sans Frontieres
WHO World Health Organisation

VL Viral Load
PDA Personal Digital Assistant
PPE Personal Protective Equipment
PCR Polymerase Chain Reaction
TB Tuberculosis



During the disinfection procedure at an outreach activity, Foya

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FOREWORD

Dear Reader,

As you will know, Ebola was the most significant medical challenge intervention we faced between 2014 and 2015; a challenge in which operational research took center stage. Indeed, we were faced with a disease of which we knew little and for which we had no cure, no means to prevent and with a lot of diagnostic constraints. Our operational research activities in the field enabled us to develop a greater understanding of the virus and how best to manage it in practice. Valuable lessons were learnt and it is vital that these lessons be retained. We must ensure that we continue to adapt our approach to managing medical emergencies of similar scale and to ensure that we do not face the same obstacles encountered during this epidemic.

This booklet provides a summary of what we learnt in relation to Ebola, and contains a review of all operational research projects carried out by our Brussels operational center, as well as the MSF Operational Research Unit based in Luxembourg.



Dr Bertrand Draguez
Medical Department Director OCB

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To the courage of all field workers who engaged in MSF Ebola control programs.



INTRODUCTION

Outbreaks of Ebola virus were first discovered in the 1970's in various central African countries, however, the West Africa outbreak that started in December 2013 has been the largest and most devastating to date.

There are five different types of Ebola virus and the West African outbreak was caused by the Zaire species, which is known to have a very high mortality rate. As of February 2016, 28,603 people have been infected and 11,301 patients died in the three most affected countries of Sierra Leone, Guinea and Liberia. A limited number of additional cases were reported in Nigeria, Mali, the United States of America, Senegal, the United Kingdom, Spain and Italy due to the repatriation of infected citizens by medical evacuation and persons entering countries well and then becoming sick from the virus causing further spread among close contacts.

The epidemic can be divided into four phases⁽¹⁾. The first phase was from December 2013 to March 2014, during which the first infections occurred in a remote region of Guinea. The inadequate health infrastructure present and the first time appearance of the virus in this region resulted in cases presenting unrecognised and therefore spread occurred undetected. The second phase from March to July 2014 heralded the confirmed spread of Ebola to the neighbouring countries of Liberia and Sierra Leone. At this time, Médecins Sans Frontières (MSF) had multiple teams on the ground responding to the escalating crisis⁽²⁾ and were vocal about the need for both national and international assistance⁽³⁾. During this phase hundreds of healthcare workers became infected and died from the virus.

The third phase of the outbreak from August to December 2014 saw an exponential rise in the number of cases across the three most affected countries, including for the first time outbreaks in major urban settings. Overstretched MSF Ebola treatment centres (ETC) were forced to turn away cases. On August 8th, the Director-General of the World Health Organization (WHO) declared the Ebola outbreak a public health emergency of international concern. The fourth phase, from December 2014 to January 2016 was characterized by decreasing numbers of new cases. This was achieved through a combination of community, national and international efforts. A number of trials for new vaccines and treatments started during this phase.

MSF in close collaboration with other actors such as the WHO and Ministry of Health (MoH), has been detecting and controlling Ebola outbreaks for decades in various African countries and uses six pillars for its approach:

Isolation of cases and supportive medical and mental health care in dedicated ETC's

Contact tracing

Awareness raising in the community

A functioning surveillance and alert system

Safe burials and house spraying

Maintaining healthcare for non-Ebola patients

These six pillars have brought previous outbreaks under control relatively quickly. The size and spread of the recent West African outbreak made it difficult for all these six control measures to be implemented quickly and as a result the virus spread.

Prior to this outbreak, the volume of scientific research available on Ebola was limited. MSF ETC's admitted over 5,200 confirmed Ebola cases, of which almost 2,500 have been cured (MSF Ebola crisis information update #19). No other national, international or non-governmental organisation has cared for more patients with Ebola than MSF. This placed MSF in the unique position of being able to use its data and experience to answer scientific questions about Ebola and how it spreads. The main objective of MSF has always been to provide medical care to those in need and this was never jeopardised by research needs.

The type of research MSF was involved in varied. Some research used routine patient data that was collected in the ETC's as part of standard care to answer questions such as which factors increased a patient's chances of survival? Other research required the collection of very specific information in order to assess for example if a trial vaccine prevented new cases of Ebola. Anthropological research required going out into the communities and asking people what they thought of Ebola and the efforts to control it.

MSF carried out research in a number of areas including epidemiology (describing the disease and its spread), vulnerable patient groups, clinical trials for new treatments, community views of Ebola, operational issues and effects of the outbreak on general healthcare. These areas of research closely reflect the six pillars of Ebola control mentioned earlier. This document aims to summarise the key findings of this research, and identify lessons learnt and knowledge gaps.



Two MSF staff dress in protective equipment before entering the high-risk area of the ETC in Kailahun

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AREAS OF RESEARCH

Clinical and epidemiological description of patients

One of the most important areas of research during an outbreak of any infectious disease including Ebola is to find out the characteristics of the patients being infected with the virus and what are their outcomes. Different strains of the Ebola virus in addition to many other factors affect patient outcomes. Such information allows medical staff to identify patient factors that are associated with a very good chance of survival and those that are associated with a high risk of dying. Staff can then provide more intensive medical care to patients at greatest risk and this is an example of relevant operational research (OR). Since MSF was the first emergency medical organization on the ground fighting this outbreak, it was involved with one of the first scientific publications regarding the emergence of Ebola in West Africa ⁽²⁾.

MSF research provided the wider medical community with detailed information on the clinical signs of patients with Ebola presenting to ETC's ⁽⁴⁻⁶⁾. This allowed other hospitals and clinics to anticipate what they should look for when assessing patients with potential Ebola. Our research showed that the level of virus in the blood is the strongest predictor of patient survival ^(7, 8) and that this can be used to counsel family members regarding expectations for their loved



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Inside the ETC in Guéckédou, Conakry

ones ⁽⁹⁾. Higher death rates from Ebola were also seen in young children and the elderly. In Guinea, investigation of various blood parameters such as haemoglobin, sodium and potassium levels and their corresponding association with survival in EVD patients was documented ⁽¹⁰⁾. In previous outbreaks of this Ebola strain, up to 90% of patients died from the disease ⁽¹¹⁾. MSF research showed early in the outbreak that the mortality rate for infected patients was generally less than 60% and that the reasons for this improved survival rate compared to earlier outbreaks was not fully understood ^(11, 12).

Several of our studies showed the spread of the virus over time across West Africa by placing the cases on maps ^(6, 7, 13) using Geographical Information Software (GIS). This is important operational research as it shows at a glance how quickly the virus is spreading in affected areas. MSF

also contributed to academic publications which looked at the genetic code of the virus from different patients in the three most affected countries. Using this information it was then possible to see how the virus jumped from one country to another at the height of the outbreak ^(14, 15).

What we learned

- The overall mortality rate in ETC's for this strain of Ebola was less than 60% during the outbreak.
- The amount of Ebola virus in a patient's blood when admitted to an ETC was the biggest predictor of mortality. The elderly and very young children also suffered an increased mortality rate from the infection.

What needs to be done next

- Further research is needed to understand why the mortality rate during this outbreak was lower than in previous outbreaks of the same Ebola strain.

Surveillance and transmission

The efficient detection of new cases of Ebola (surveillance) and understanding how the virus was transmitted from person to person were crucial for controlling the outbreak. MSF research showed that as in previous outbreaks, the virus was predominantly transmitted by either direct contact with infected persons, indirect contact with infected persons through contaminated body secretions such as vomit or during traditional burials of patients who had died from EVD ^(16, 17).

A single case of sexual transmission of Ebola was identified in early 2015 using both a detailed look back exercise and comparing the genetic code of the virus between the cases ⁽¹⁸⁾. It is highly likely that during the outbreak, sexual transmission of Ebola accounted for only a small proportion of the overall cases. Sexual transmission may also be responsible for the flare up of cases that occurred after the declaration of the end of the outbreak in Sierra Leone and Liberia. Additionally, it was discovered that some male survivors of Ebola could carry fragments of the virus for prolonged periods in their semen. It is not known if these fragments can in general start new infections in sexual contacts. The fragments may simply be dead pieces of virus and further research is continuing in this area to clarify the risks. MSF has repeatedly stated that it is important not to stigmatize survivors of Ebola as this will cause any new cases to avoid seeking help. People are less likely to disclose they are suffering symptoms of the virus when they witness how badly survivors are treated by communities ⁽¹⁹⁾.

Certain regions of West Africa have a long-standing surveillance system in place for Lassa fever, a virus that can cause both fever and bleeding but does not have the high mortality rate of Ebola. In Bo district in Sierra Leone, MoH



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A GIS (Geographical information systems) Officer studies the origins of confirmed and probable patients in Foya

and other actors managed this Lassa surveillance system and during the early phase of the Ebola outbreak, the Lassa fever surveillance team was able to identify and follow up a proportion of Ebola cases, but as the outbreak grew in size, the surveillance team was overwhelmed ⁽²⁰⁾. The loss of this surveillance capacity allowed further transmission of Ebola to go undetected in the area.

At present, for Ebola patients, it is not fully understood at what time different body fluids (blood, urine, semen and breast milk) start to carry the virus and how good the virus is at passing from these different fluids and infecting new patients. MSF in collaboration with laboratory partners is trying to answer these questions by using samples it collected during the medical care patients received in ETC's ⁽²¹⁾. Such information will help us better understand how the virus spreads between people and for how long they remain infectious.

What we learned

- There was only one Ebola case confirmed to have been transmitted via sexual contact.
- Various body fluids from Ebola patients such as blood, saliva, urine, amniotic fluid, and breast milk contain the virus at different levels during the course of the disease.

What needs to be done next

- We need to better understand how infectious the virus is in body fluids such as urine, breast milk and semen. This will allow a greater understanding of how the virus transmits from person to person in an outbreak setting and for how long they are infectious.

Vulnerable groups

During any humanitarian emergency there are certain groups that are more vulnerable than others. MSF always prioritizes providing medical care to these vulnerable groups and looks to find new ways to deliver better care. Particular groups focused on during the Ebola outbreak were pregnant women, children, the elderly and survivors of Ebola.

Pregnancy

MSF ETC's admitted pregnant women and produced detailed medical guidance on caring for them ^(22, 23). Importantly, our research showed that even when a pregnant woman recovered from Ebola, her baby and the fluid surrounding it can still contain the virus ⁽²⁴⁾. Therefore, at delivery of the baby, there is considerable risk that those assisting could be infected ^(25, 26). Consequently it was proposed that pregnant women discharged cured from Ebola should be readmitted to the ETC when labour starts ⁽²⁷⁾. MSF also identified the possible risk of Ebola passing from an infected mother to child through breastfeeding and recommended that breastfeeding be stopped and not restarted ^(28, 29).

Children

Children are made vulnerable by either contracting the virus or from their parents dying of Ebola causing them to become orphans. The MSF ETC in Guinea showed that children being admitted presented a number of challenges including the unavailability of paediatric drug formulations and difficulties associated with placing intravenous lines in the very young. Children, especially the younger ones without any Ebola confirmed caretaker accompanying them posed particular concerns because it was not possible to provide them with continuous care due to the limitations of wearing PPE. Therefore, unless other patients stepped in, these children remained unaccompanied between ward rounds making the provision of sufficient oral rehydration for them extremely challenging. The mortality rate was shown to be higher for younger children, especially children under 12 months of age ⁽³⁰⁾.



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An Ebola survivor undergoes an eye test in Liberia, as part of medical and mental health support that MSF provides to Ebola survivors

Survivors

Survivors of Ebola discharged from an ETC have gone through the unique experience of seeing approximately one half of the admitted patients die from the disease. They are also likely to have had close family members die from the infection. Survivors face many challenges after leaving the ETC which can be broadly divided into 2 categories; community response to returning survivors and the mental and physical health issues following Ebola infection.

Community response to returning survivors

MSF staff collected data to better understand how communities responded to the return of survivors. While some survivors were welcomed back eagerly by their communities, others experienced marginalization. It was noted that when survivors were accompanied back home with MSF staff they were generally readily accepted by family, friends and neighbours. However, male survivors were at particular risk of being stigmatized because some members of communities believed they could infect women through sexual intercourse ⁽³¹⁾. Male survivors were even described as "atomic bombs" with the potential to infect "the whole nation" ⁽³¹⁾. Some community members suggested creating "Ebola camps" to hold male survivors for several months to ensure no further spread of the virus ⁽³²⁾. Such stigmatization can have serious effects on already traumatized individuals. Additionally some survivors found it difficult to gain employment after returning home due to certain employers viewing them as a risk for spreading Ebola.

Mental and physical health issues

MSF employed psychology teams throughout the outbreak to follow up and support the mental health of survivors. In Sierra Leone, MSF found that over one fifth of survivors were at high risk of developing post traumatic stress disorder ⁽³³⁾. Similarly, in Liberia we found that survivors who were discharged several weeks previously had persistent physical symptoms such as muscle and joint aches, fatigue and eye problems. Additionally, a proportion of these same patients suffered from depression, post traumatic stress disorder and stigmatization ^(34, 35).

Elderly

Our research identified the elderly as having a high mortality rate, especially those greater than 50 years of age ⁽⁷⁾. The reasons for this are unclear, however the elderly are more likely to have a weaker immune system and other chronic diseases which may make them more susceptible to dying from the infection. MSF supports the need for more research on why the elderly have a higher mortality rate and what can be done to reduce it in future outbreaks.

Pregnant women, children, the elderly and survivors from Ebola require specific care and close follow up post discharge. Such care can be improved using MSF research.

What we learned

- Pregnant women who recover from Ebola can still harbour the virus in the baby they are carrying and the fluid surrounding the baby (amniotic fluid). Therefore, for these women it is important that they are readmitted to the ETC during labour to allow the safe delivery of the baby while minimizing the risk of infection to those assisting the birth.
- Some survivors of Ebola suffer serious mental and physical health issues such as depression and eye complaints that persist after discharge from the ETC. It has become accepted that such survivors require specialised follow up care.

What needs to be done next

- Long term follow up of Ebola survivors is needed to understand what proportion of them suffer medical complications. We also need to know the severity of these complications and how they can be best treated in local settings.

Clinical trials

As the outbreak intensified throughout 2014, there were increasing calls for experimental treatments to be made available for patients with Ebola in West Africa. It is standard practice that experimental treatments for any disease are first tested in a trial setting to see if they are effective or not. When found to be beneficial, the treatments are then used more widespread. Historically, MSF has not been involved with working on experimental trials during a humanitarian emergency. This policy changed with the West African outbreak because EVD had such a high mortality rate and MSF ETC's were admitting such a large proportion of all Ebola cases. Consequently, MSF in collaboration with the WHO and other agencies assisted with the trials of experimental treatments at various locations.

The vaccine trial that started in Guinea has shown very promising results. MSF was a co-author on an important research paper which indicated that almost all people who received the vaccine at the appropriate time were protected from developing EVD⁽³⁶⁾. Although it is important to remember that a vaccine cannot treat those who are already suffering from the infection, it can help prevent people from getting the virus in the first place if they are vaccinated in time. This vaccine and others like it offer the hope of not only stopping this outbreak but also future ones caused by Ebola Zaire. MSF in partnership with other organisations highlighted that a trial drug called Favipiravir was of some benefit to patients who presented to ETC's with a low level of Ebola virus in their blood but not to those with a high level^{(37) (38, 39)}.

In a previous outbreak of Ebola decades ago, the blood from survivors (known as convalescent plasma) was transfused into patients who were sick with the disease. At that time it was suggested this improved the chances of survival for patients. MSF as part of a team of national and international organizations commenced the largest ever trial of convalescent plasma in Guinea in early 2015. The results of this trial showed there was no significant increase in survival among those who received the convalescent plasma compared to those who did not⁽⁴⁰⁾.



© Laura Bianchi

Ebola frontline workers in Conakry receive the rVSV-EBOV experimental vaccine

The challenges facing MSF when starting vaccine, Brincidofovir, Favipiravir and convalescent plasma trials in the middle of an emergency humanitarian situation were formidable. Although, the most important issue was to make sure patients and the community understood and accepted the benefits of using trial drugs for an infection with such a high mortality rate. At all times patients were given the right to refuse if they so wished. Ethics approval for each trial was obtained from the relevant national and international organisations.

MSF anthropologists went into communities in affected countries and asked them what they thought about clinical trials for Ebola patients. The predominant response was that people welcomed trials: "anything that can work, we want it"⁽⁴¹⁾. People also demanded that anybody who needs the trial drugs should get them and not restrict them to the rich only: "I want it to reach the common man from bottom to top". It was noted that those interviewed believed that providing clinical trials at ETC's would encourage people with Ebola symptoms to attend because such trials offered the possibility of cure: "If you bring medication, people will be encouraged to come. You can make it if you get to the hospital". Throughout this process, community members repeatedly stated the importance of the entire trial process remaining transparent to both patients and the wider community so as to avoid rumours⁽⁴¹⁾.

What we learned

- The vaccine trial in Guinea showed that contacts of Ebola cases who received the vaccine were significantly less likely to develop the disease than those contacts who did not receive the vaccine.
- The trial drug Favipiravir showed some benefit for patients who presented to ETC's with low levels of virus in their blood.
- Convalescent plasma did not significantly increase the chances of survival for Ebola patients who received it.
- Communities are generally receptive to drug trials for a disease such as Ebola with a high mortality rate and no cure when all information is shared openly.

What needs to be done next

- In any future outbreaks of Ebola it is necessary to be able to commence the use of appropriate trial drugs as soon as possible. An international clinical trials agreement for humanitarian emergencies must be put in place to facilitate this.
- Although convalescent plasma was shown not to significantly increase the chances of survival, this study did not take into account the amount of neutralising Ebola antibody in the plasma. It is necessary to further analyse the results to see if those patients who received convalescent plasma with high levels of antibody did better than those who received plasma with low levels of antibody.

Understanding the community

MSF anthropologists had the important role of finding out what the affected communities thought of the Ebola virus and government control measures such as quarantine. This research allowed MSF to identify areas of misunderstanding and rumour within the community. Health promotion messages were then targeted to address these knowledge gaps. In addition, anthropologists were crucial for identifying the beliefs and behaviours within communities that facilitated further spread of the Ebola virus.

Cremation was used for patients who died from Ebola in Monrovia only and was not well received by some members of the community. West African funerals allow families to say goodbye to their recently deceased family member and graves provide a place where they can visit regularly to pay their respects. Funerals are also a social gathering where people can meet and discuss crucial issues such as land disputes, inheritance and other transactions ⁽⁴²⁾. Replacing funerals with cremation denied families and communities these opportunities for shared grieving. Interviewees accepted that during the height of the outbreak when there were a large number of infected dead bodies, cremation was needed to reduce spread of the virus ⁽⁴³⁾. However, they resented the way this order continued to be enforced by senior government officials long after the peak of the epidemic when more socially acceptable forms of safe burial could be used for the reduced number of dead bodies. Respondents noted that "rich families" were able to pay for their loved ones to be buried in a private cemetery while the poor, who could not afford the fees being charged by illegal burial teams, had to send the body to the crematorium ⁽⁴⁴⁾. Some participants voiced their support for illegal burials: "I'd do the same, just pay someone to dig the grave and you know where your beloved is" ⁽⁴³⁾.

In August 2014, the Liberian government quarantined an entire neighbourhood of the capital Monrovia using military personnel in an attempt to prevent further spread of the virus. This was not well received by the community:



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A health promoter talks to village residents about health issues during a MSF outreach mission, Sierra Leone

"We didn't understand the logic, instead of helping us with clinics and ambulances, they pushed us in. What were we supposed to do?" ⁽⁴³⁾. MSF did not support the use of quarantine for controlling the outbreak because it was not viewed as an effective measure. The state imposed use of quarantine for 21 days for close contacts of patients with Ebola was recognized by some communities throughout the affected countries as something that could prevent spread of the infection ⁽⁴⁵⁾. Research showed that one of the main issues people had with quarantine was the chaotic way it was implemented. Individuals under quarantine sometimes only received food and water intermittently by the designated organization thus forcing them to disobey the imposed isolation ⁽⁴³⁾. Those under quarantine were at risk of stigmatization from the surrounding community but this sometimes ended when the quarantine phase was over and the person remained healthy ⁽⁴⁵⁾.

Anthropology research provided insight into communities that guided the outbreak control measures of MSF and other organizations working in the field.

What we learned

- State imposed cremation of Ebola cases in Liberia and quarantine of contacts in Sierra Leone caused significant fear and mistrust among affected populations which sometimes resulted in behaviour that increased the spread of the virus.

What needs to be done next

- In any future flare ups of Ebola, it will be necessary to incorporate community led solutions for controlling the outbreak.

Operational challenges

This Ebola outbreak posed many challenges not only for MSF but also for other actors involved in the response. MSF used research where feasible to address these challenges for the benefit of patients and staff.

Recording patient information

Recording clinical notes in an ETC was a complex process. Paper based records were completed by staff in the high risk zone while attending patients but these paper records could not be sent to the low risk zone for review and entry onto a database because of the risk of transmitting infection. As a result staff from the high risk zone had to shout the results of ward rounds across the fence to staff in the low risk zone on the other side who recorded the information on clean paper. This process was slow and sometimes inaccurate, which led MSF to trial a scanning system based on mobile phones mounted on custom made stands and positioned in strategic places across the ETC ⁽⁴⁶⁾. Clinical notes from the high risk zone could then be scanned and transmitted over a secure wireless network to a printer in the low risk area. This new method improved the quality of data being collected and reduced the time required for transmitting information. Additionally, infection risks were minimized ⁽⁴⁶⁾. In Liberia, MSF staff commenced using personal digital assistants (PDA) to record clinical information during ward rounds in the high risk zone. This information could then be transmitted in real time to the medical office in the low risk zone, negating the need for paper. It was found that PDA's reduced the overall time staff had to spend recording information during ward rounds ⁽⁴⁷⁾. The novel use of technology for recoding information is dependent on having appropriate technical expertise available to fix it should it fail in an emergency humanitarian setting ⁽⁴⁷⁾.



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Staff testing one of the Clinical Management Tablets at the Magburaka ETC



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Testing a patient's blood for Ebola in Kailahun

Laboratory testing

The traditional way of diagnosing Ebola involved taking a blood sample from the patient using a needle and syringe (venipuncture). This blood sample was then tested for the Ebola virus using a technology called polymerase chain reaction (PCR). Sometimes healthcare staff found it very difficult to obtain a blood sample by venipuncture from very young children who were also dehydrated. Occasionally patients refused to have venipuncture performed due to religious or cultural reasons ⁽⁴⁸⁾. Staff that carried out this procedure while wearing personal protective equipment (PPE) were also at risk of needle stick injuries that could in turn cause them to become infected with the virus. Fingerstick tests are used to check patient's for malaria by making a small puncture in the skin of the fingertip with a lancet and then squeezing out a drop of blood for analysis. Fingerstick blood samples are much easier, faster and safer to take than venipuncture samples. MSF questioned whether fingerstick samples could be used instead of venipuncture for diagnosing EVD in ETC's. MSF staff in Guinea collected data on patients being screened for admission using both venipuncture and fingerstick blood tests and found that fingerstick samples were able to detect 87% of the Ebola cases confirmed using venipuncture samples ⁽⁴⁸⁾. As a result of this research it was recommended that fingerstick blood sampling, while less accurate than venipuncture for diagnosing Ebola, could be used in situations where it was not possible to perform venipuncture.

The PCR test used to diagnose EVD is very accurate, that is, it is very good at identifying those people who have Ebola, while excluding those who have not. Very rarely, the PCR test can give incorrect results. MSF in collaboration with other organisations produced research that highlighted an Ebola case in Monrovia with a false negative PCR result ⁽⁴⁹⁾.

A false negative result occurs when the PCR test indicates that the virus is not present while in reality it is. Research such as this underscores the need to always interpret test results in combination with the clinical and epidemiological history of each patient.

Regarding the PCR test for Ebola, the time taken between obtaining a blood sample and getting a result can be considerable ⁽⁵⁰⁾. This is due to a number of factors including the location of the laboratory in relation to the ETC. MSF assessed the feasibility of using a different Ebola test (called the Xpert Ebola Assay) and locating the testing device within the ETC. It was found that using the Xpert Assay compared to traditional PCR testing reduced the waiting time between sampling and result notification by over 50% ⁽⁵⁰⁾. This is a significant improvement in turnaround time for test results especially for those patients waiting in the suspect area to be admitted or discharged.

Triage

When patients first arrived at an MSF ETC, a doctor or nurse at triage assessed them. This step was used to figure out which patients presenting were likely to have Ebola or not. Those who met the criteria of a suspect case using the WHO/MSF case definition were admitted to the suspect area of the ETC for blood testing. Individuals not fulfilling the case definition were discharged from triage. It is evident that the triage step was a very important one. If it was not carried out appropriately with an accurate case definition, then some potentially infected persons could be sent home while non infected ones could be admitted to the suspect area. Such a scenario posed a threat for further spread of the virus ⁽⁵¹⁾. MSF contributed to research that investigated which combination of clinical signs and history of contact best discriminated between cases and non – cases ^(51, 52). What is especially lacking is an accurate point of care Ebola diagnostic test that staff could use in the suspect area to find out there and then if a patient has Ebola or not ⁽⁵³⁾.



© Martin Zinggi

ETC staff members hands water sachets to new people in the triage, Foya

Infection control

Preventing the spread of Ebola virus within the ETC's to staff and other personnel was a priority during the outbreak. Strict procedures were put in place to ensure MSF staff had access to PPE and appropriate training on how to put it on and remove it in a safe manner. The minimum level of PPE that is required when treating Ebola patients is still not fully understood. In general, the higher the level of PPE, the more difficult it is for staff to attend patients in tropical environments due to heat illness. MSF participated with a number of organizations to explore what the optimal PPE should be and this research is ongoing at present ⁽⁵⁴⁾.

Infection control was critical for patients admitted from triage into the suspect area of the ETC. While in the suspect area, patients had blood tests performed to check for the presence of Ebola with a positive test causing the patient to be admitted to the confirmed ward of the ETC and a negative test resulting in discharge from the facility. Therefore within the suspect area, there were patients with and without Ebola present at the same time. If infection control measures were poor in the suspect area, it is possible that negative cases awaiting blood test results could contract the virus from positive cases also awaiting test results. MSF researched this important issue and found there was no evidence of it occurring in MSF ETC's ⁽⁵⁵⁾. Plexiglass partitions were introduced to ETC's during the outbreak. This allowed staff to assess how patients were progressing without having to put on PPE. The plexiglass partitions facilitated greater interaction between patients and staff and also strengthened infection control measures within ETC's.

It is not only in ETC's where infection control was important. During the height of the outbreak in Monrovia, when there was no bed availability in ETC's, MSF decided to distribute over 65,000 Ebola protection and disinfection kits to households, frontline workers and other targets in the poorest areas of the city ⁽⁵⁶⁾. These kits included a bucket, chlorine, surgical gown, mask and gloves and were to be used while caring for any sick person in the community or to handle any dead body while awaiting the ambulance to arrive. The kits were essentially a way of creating infection control procedures in the community at a time when there was no bed availability in ETC's. In close association with the distribution of the kits, MSF carried out intensive health promotion activities in the community to ensure people understood how and when the kits should be used. MSF follow up research indicated that 99% of community respondents agreed that the kits were useful and had no problem using them ⁽⁵⁶⁾.

The Hazard Analysis of Critical Control Points (HACCP) is a tool used in other disciplines such as the food sector to prevent contamination by biological or environmental material. HACCP provides a systematic framework for identifying what could go wrong and for actively planning how to prevent it. MSF in association with other researchers found that the HACCP protocol could potentially be used in the community setting as an infection control measure to reduce the risk posed by human waste in areas of Ebola transmission ⁽⁵⁷⁾.

What we learned

- The use of Personal Digital Assistants (PDA's) for recording patient information in an Ebola Treatment Centre (ETC) was shown to be more efficient and safer than paper based methods.
- Fingerstick blood tests were found to be slightly less accurate than venipuncture tests for detecting Ebola virus. However, fingerstick tests are easier to perform and act as a suitable alternative when venipuncture is not possible.
- The waiting time between patient sampling and results notification was reduced by over 50% when using the Xpert Ebola assay for detecting the virus compared to the traditional PCR technique.
- Infection control procedures in the suspect zone of an MSF ETC were adequate to prevent transmission of infection between individuals with and without EVD while awaiting blood test results.

What needs to be done next

- Further research is needed to develop a fast and reliable point of care test for the Ebola virus so that patients can be tested safely and quickly for the disease.
- It is necessary to investigate what minimum level of PPE is required to prevent Ebola infection while at the same time being suitable to wear in tropical environments.

Effects of the outbreak on non-Ebola healthcare

Prior to this outbreak, Sierra Leone, Guinea and Liberia had very low ratios of healthcare staff to their respective populations. The consequent onset of the epidemic had a devastating effect on national health care workers with hundreds succumbing to the infection over the course of the outbreak⁽⁵⁸⁾. Such a loss of already scarce staff had a severe impact on how health services of affected countries could meet the non-Ebola health needs of their citizens.

Ebola has been compared to HIV in many articles, however while the characteristics of the two viruses are quite different, they are both similar in how they affected all sectors of society far beyond the health system ranging from the economy to education and also cultural practices such as circumcision for HIV and burials for Ebola⁽⁵⁸⁾. It was noted in various studies that during the Ebola outbreak there was a major drop in clinic attendance of new HIV positive diagnosis and new HIV infected patients entering care in the affected countries⁽⁵⁸⁾. This was due to a combination of: patients being afraid to attend clinics because of the known risk of catching Ebola, clinics closing because of a lack of staff and clinics reluctant to see new patients who may have symptoms compatible with Ebola.

During 2014, MSF in Monrovia undertook to research the effects of the outbreak on maternity care and general non-Ebola health care. The findings suggested that there was an important decrease in the number of facilities open and for those which remained open, there was a reduction in patient attendance and deficits with infection control procedures⁽⁵⁹⁾. A modelling exercise by MSF staff estimated that the maternal mortality rate over this period was potentially 15 times that of the background rate giving an indication of the detrimental effect Ebola had on normal maternity care services in Monrovia⁽⁵⁹⁾. In a large primary



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Access to healthcare in Monrovia is limited due to Ebola outbreak

health care centre in rural Sierra Leone, MSF showed that there was a 36% drop in attendance of children under the age of 5 years in 2014 compared to the previous year⁽⁶⁰⁾. Additionally this research showed that the proportion of children under 5 attending the emergency department in severe clinical status was greater during the epidemic period. Similarly, on the topic of non-Ebola care, MSF has raised concerns that the control of Tuberculosis (TB) in the region may be jeopardised by focusing solely on Ebola⁽⁶¹⁾ and that operational research (OR) is required to document this and suggest strategies for better sustaining TB care during future epidemics.

It is evident from MSF's experience⁽⁶²⁾ in the affected countries that basic non-Ebola health care including maternal⁽⁶³⁾ and child health was adversely affected during the epidemic. The Ministries of Health in the affected countries, supported by WHO and MSF, are currently running operational research courses to study the impact of the outbreak on health systems.

What we learned

- Maternal and child health were adversely affected during the Ebola outbreak with a documented increase in maternal mortality in Monrovia and a decrease in attendance of children under five in a primary health centre in Sierra Leone.

What needs to be done next

- Strategies need to be developed for sustaining normal healthcare during future epidemics.

Fundamental questions about the virus

The West African outbreak has raised many fundamental questions about the Ebola virus and MSF research has addressed some of them. For example, how the Ebola virus affects our immune system is not fully understood. Addressing this, MSF in association with other institutions was a contributing author to a scientific publication that showed a certain molecule (called CTLA-4) caused the immune system to weaken and was over produced in those patients who died from the infection ⁽⁶⁴⁾. It is research such as this that allows scientists to develop strategies for cures.

Another fundamental issue was that different laboratories used different types of PCR tests which can give varying values for the amount of virus (viral load) present in the blood. As a result, sometimes it was difficult to compare viral load results between laboratories for research purposes. MSF in partnership with others has investigated all the different types of PCR technology used and advocated that standardized tests be employed so that viral load results can be compared between laboratory sites ⁽⁶⁵⁾.

The media and the medical literature have recently discussed that Ebola may become endemic in West Africa,



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Blood samples being tested for Ebola, Guéckédou

meaning that the virus would constantly be present in the affected population. This is an important point to highlight but MSF in collaboration with other international experts reported that this is very unlikely to occur due to the way the virus is transmitted, how it changes over time and how unsuitable humans are as hosts ⁽⁶⁶⁾.

Answering fundamental questions such as these about the virus is key to controlling it.

What we learned

- Different laboratories used different types of PCR test which gave varying values for the amount of virus (viral load) present in the blood.

What needs to be done next

- A recognised standardised PCR test used by all laboratories would allow viral load results to be compared between sites.

Healthcare workers

An area of neglected research is assessing what effect working in an Ebola emergency had on healthcare staff. These professionals were tasked with treating EVD patients who had a mortality rate of at least 50% in challenging clinical settings while at the same time trying to avoid getting infected themselves. MSF psychologists have investigated the burden placed on health workers and found that “risk of contagion, uncomfortable protective clothing, work overload, danger, facing death and people with great suffering” were some of the daily issues faced by these workers ^(67, 68). This information allowed MSF to offer tailored counselling to all Ebola emergency workers during and after their service. An area of further research regards what effect high staff turnover had on the operation of ETC’s. During the height of the epidemic it was common for certain staff to spend a maximum of four to six weeks in the field and then return home. Such changeover of personnel had the potential to cause disruption to the efficient management of centres.



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MSF psychosocial support assistant Sionnie.

What we learned

- Health professionals in ETC’s faced many challenges, both physical and psychological, while attending patients.

What needs to be done next

- A greater understanding is required about the risk of contagion for staff in ETC’s.
- Develop comprehensive occupational health policies for both national and international staff.



An Ebola survivor holds his sick daughter while waiting at the triage in MSFs ETC in Paynesville

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DISCUSSION

MSF research on Ebola as described in the previous sections has been significant. Most of this activity has been operational research (OR) that aims to answer pressing questions from the field. However, OR requires the collection of accurate routine data and one of the issues with the large number of MSF ETC's spread across three countries was that information was not collected in a standardized way. This led to difficulties later on when trying to amalgamate and analyze patient data. Additionally, clinical interventions such as the use of intravenous fluids were not recorded systematically across ETC's. This proved to be a lost opportunity as it was not possible to retrospectively assess what effect using this intervention and others had on patient outcome. Although it must be recognized that during the height of the outbreak when limited healthcare staff were under severe pressure, not all routine clinical information could be recorded. The use of PDA's has the potential to overcome this problem with future outbreaks.

The research produced by MSF was mostly decided by returning field staff. These individuals noticed particular operational issues while working in the field and then committed to carrying out research to address them on

their return. They were assisted by the operational research unit of MSF and provided with the relevant routinely collected patient data. Such a method for selecting research topics can make the results very relevant for field teams caring for patients but can also bias research output by only selecting those topics that returning individuals bring forward. To balance this, the MSF operational research unit also supported the development of research questions that needed to be answered during the course of the outbreak. The combination of allowing both field and office staff to develop and carry out research created a productive environment for scientific enquiry that had a real benefit to patients. MSF also streamlined its research ethics approval process which still remained robust and allowed researchers to gain ethical consent for their work in a reasonable timeframe. Important findings from operational research were disseminated back to the field in a timely and appropriate manner to maximize patient welfare which is the primary goal of such activity. However, when research was then submitted to scientific papers for more widespread distribution of findings, authors faced the challenge of finding journals that would review, accept and publish the results in an appropriate timeframe. Some journals had the

capacity to make quick decisions about publication while others were much slower and delayed the eventual dissemination of research to the scientific community by several months. Of note, some MSF scientific publications were delayed because authors were slow to finalise manuscripts due to competing work priorities. As a result of the obstacles to publication that can occur with traditional journals, MSF should consider setting up its own web based open access scientific journal that can release important research findings in a shortened timeframe while maintaining scientific standards.

The trials for vaccines, favipiravir and convalescent plasma were challenging to introduce in an emergency humanitarian setting and required impressive teamwork by all involved. Regrettably, even though the trials were fast tracked compared to traditional timeframes, they were commenced very late in the outbreak when the numbers of cases were dwindling making it difficult to establish efficacy. MSF has advocated strongly that protocols and ethical guidelines for clinical trials during emergencies be pre-approved during the inter-epidemic period so when the next emergency occurs, trials can commence much sooner⁽⁶⁹⁾. In tandem with the clinical trials, one of the most valuable tools for fighting the Ebola outbreak but which is still not yet available is an accurate point of care test for the infection. This would allow quick and accurate results for patients and streamline the triage process at ETC's.

Anthropological research has played an important role in helping MSF understand what the affected communities think of Ebola and the methods used to control it such as ETC's, quarantine and cremation. In addition, anthropologists were crucial for identifying the beliefs and behaviours within communities that facilitated further spread of the Ebola virus. These insights allowed MSF to tailor its activities to best suit the communities it was operating in. An example of where anthropology can be extremely useful is the stigmatization of male survivors due to the possibility of them causing further spread of the virus through sexual transmission. Only when health promotion teams have a deep understanding of community fears can they effectively address issues such as male survivor stigmatization. One notable issue with anthropology research during this outbreak was the delay in starting it due to both operational and human resource issues.

MSF research has shown that survivors can suffer from serious medical complications in the short term. Accordingly, there needs to be comprehensive follow up of a large cohort of survivors to better understand these complications and how they evolve over time.



An Ebola survivor 'signs' the wall at ELWA 3, Monrovia

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CONCLUSION

MSF has produced an important collection of both published and unpublished research on the Ebola outbreak in West Africa. An indicator of the relevance of this research can be found in how other organizations used MSF research and guidelines to direct their activities in the affected countries. Importantly, the categories of MSF research closely correspond to the six pillars of Ebola outbreak control described in the introduction. Our research work is still ongoing, and includes studies on the impact of Ebola on local health systems. Therefore a future update of this booklet will be necessary.

Research allows MSF to continually develop its guidelines and assess if new approaches are more effective than the ones currently in use. Research is always aimed either directly or indirectly at improving the care we provide to those in need. The current model for deciding research topics within MSF is targeted towards addressing issues in the field. This is appropriate for an emergency medical organization.

This Ebola outbreak and all previous ones have shown the urgent need for accurate rapid diagnostic tests, effective treatments and a working vaccine. International research institutions must continue to prioritise these areas of investigation even though this outbreak has ended. Now is also the appropriate time to agree ethical clinical trial protocols for the next humanitarian/medical emergency.

Finally, how the international community can better respond to a major infectious disease outbreak is an area of research that needs to be urgently addressed. MSF has repeatedly pointed out the deficiencies of governments and agencies during this outbreak and strongly calls for the creation of a functioning international rapid response capability for infectious disease outbreaks ^(70, 71).

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