United States Senate Committee on Foreign Relations
Subcommittee on Africa and Global Health Policy

Hearing: A Progress Report on the West Africa Ebola Epidemic

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Testimony Prepared by
Sophie Delaunay
Advisor, Doctors Without Borders/Médecins Sans Frontières (MSF) USA

Thank you Chairman Jeff Flake, Ranking Member Edward Markey, and Members of the Subcommittee for providing Doctors Without Borders/Médecins Sans Frontières — also known as MSF — the opportunity to share our perspective regarding the Ebola outbreak in West Africa, and some of the lessons MSF has garnered in its wake.

The Ebola Virus Disease (EVD) outbreak in West Africa was the most significant global medical challenge MSF faced between 2014 and 2015. As we speak, recent cases declared in Guinea and Liberia attest to the continued challenges posed by the virus.

MSF's response to this outbreak has been unprecedented, and prompted one of our biggest emergency interventions in the 40 years MSF has been operational internationally. MSF responded across the region in Guinea, Sierra Leone and Liberia, but also in Mali, Senegal, and in Nigeria, and cared for one third of all infected patients throughout this outbreak. From March 2014 to December 2015 – MSF set up and managed 15 Ebola management centers, with 40 to 250 beds in each facility, and also provided Ebola management training to national governments, international responding agencies – including the CDC, U.S. Public Health Service and the 101st Airborne Division – and other non-governmental organizations.

Across many sectors, valuable lessons were learned in the past two years, and it is vital that these lessons be acted upon. Needless to say, we also learned many of our own lessons in this process. Today, I am going to share with you MSF's perspective regarding one specific issue: the state of biomedical research and development (R&D). Notably, Ebola not only revealed existing challenges in the current R&D system; but allowed us to learn lessons that we think are also applicable to a large number of other public health priorities, from tuberculosis, to antibiotic resistance to Zika.

Ebola starkly illustrated how critically important it is to develop tools for infectious diseases before an outbreak occurs, as well as how challenging it can be to respond when adequate tools aren't available. This was not just an Ebola problem, though; it's an R&D problem, a systemic problem. And the consequences should really come as no surprise. Ebola was discovered nearly 40 years ago, but only after the outbreak devastated thousands of lives across West Africa and reached the U.S. and Europe, were significant R&D efforts launched to deliver tools to prevent and treat the disease.

Historically, Ebola has primarily affected rural populations in sub-Saharan Africa, and therefore the development of tools to prevent, diagnose, or treat the disease has not been a priority. Almost no R&D efforts were focused on Ebola until the mid-2000s, when the virus was identified as a potential bioterrorism threat in several countries. Thereafter, the U.S., Canada, and a few other governments began supporting some basic research projects for Ebola.

However, the primary objective was to protect citizens of the countries sponsoring the research, not necessarily to address the needs of people affected by the disease where it occurs, in Africa. Therefore, crucial characteristics, such as product affordability or user-friendliness in resource-poor settings, were not really taken into consideration. Moreover, some of the public funding for this research dried up due to national level budget cuts, and several potentially promising treatments and vaccines stalled in the early stages of development without a sponsor to take them forward.

When the current outbreak started, research was incomplete and products had not been developed, despite the earlier public investments. Following the introduction of Ebola cases on U.S. and European soil, a number of trials for new vaccines and treatments were initiated. The beginning of these trials, however, also coincided with decreasing numbers of new cases.

Today, where do we stand when it comes to preventing, diagnosing or treating Ebola? Should there be another Ebola outbreak tomorrow, or an outbreak of another deadly and neglected pathogen, will we be better equipped to provide relief and treatment to the people affected by the disease? How can the R&D efforts be improved upon?

I would like to address a few of these questions now:

Firstly, in the area of **diagnostics**: the traditional Lab-based polymerase chain reaction (PCR) test used to diagnose EVD is very accurate, but the time taken between obtaining a blood sample and getting a result can be considerable[1], and can take several days in some cases when samples need to be shipped from remote areas, as we have seen in West Africa. By using other types of accurate tests that can be positioned in more peripheral settings (such as the

[1] Van den Bergh R, Chaillet P, Sow MS, Amand M, van Vyve C, Jonckheere S, et al. Feasibility of Xpert Ebola Assay in Médecins Sans Frontières Ebola Program, Guinea. Emerg Infect Dis. 2016;22(2):210-2106

GeneXpert assay), our teams were able to reduce the time needed between sampling and result notification by 50%. Considering that the earlier a patient is treated, the more likely they are to survive, this is significant progress. The diagnostic process, however, is still time consuming and labor intensive. **What is still lacking today is an accurate and rapid point of care Ebola diagnostic test that caregivers could use in the triage area to find out immediately whether a patient has Ebola or not.**

Secondly, regarding **therapeutics**, three main types of products were tested or used in the treatment of patients: antibody-based products (i.e. ZMapp, convalescent serum), antiviral products (i.e. favipiravir, brincidofovir), and to a lesser extent, commercially available drugs repurposed for Ebola due to demonstrated *in vitro* activity (i.e. amodiaquine). None of the trials have been fully conclusive. In many cases, due to the decreasing numbers of infected individuals available to participate in trials, the sample size was just too small to lead to definitive conclusions.

The most promising results were found with ZMapp (licensed to Mapp Biopharmaceutical). There are on-going discussions in the United States to offer ZMapp under an "expanded access protocol" until it reaches licensure. However, other limitations for its use remain – including the potential high price of ZMapp and the limited production capacity. MIL77, a biosimilar of ZMapp which is produced in China is more likely to be available in large quantities and potentially at a lower cost. We are also now seeing many second generation drugs in the pipeline, but these products are unlikely to pass through the necessary trials before the next outbreak. One question, in this case, is whether it could be possible to rely exclusively on data in animals and in healthy volunteers to approve new treatments for Ebola.

Regarding **vaccines**, the good news is that there are now many more vaccine candidates in the pipeline. One of them – rVSV-ZEBOV acquired by Merck – is currently the most advanced candidate. Yet, even if scientists are able to confirm its efficacy and safety, it still will not be the perfect vaccine for Ebola due to several significant limitations. The vaccine currently needs to be stored at -80°C (-112 Fahrenheit); it protects only against Zaire Ebola virus and not for other Ebola species or other filoviruses such as Marburg; the duration of its immunity is unknown; and the management of recorded side-effects – such as post-vaccination fever – will constitute a challenge during an epidemic.

As you can see, and despite a remarkable mobilization in accelerating Ebola research and development, current solutions are not a panacea. From my preceding assessments, we can conclude that, if there were another outbreak of EVD tomorrow, the tools will surely help but we cannot ascertain that we will contain the virus or save the lives of most patients.

Lastly, there are still a number of crucial questions related to the course of the disease itself. For example, how long does the virus linger in body fluids? This question leads to complications in a significant number of survivors and to the potential risk of sexual transmission several months after a patient could be otherwise confirmed as Ebola-free. More research is needed.

There are other sequelae for Ebola survivors that require further research, including post-traumatic stress disorder.

MSF would like to see changes in the way biomedical R&D is conducted, including by pursuing the following:

1. Invest in patient and needs-driven R&D before the next epidemic;
2. Test these candidates and start clinical trials as early as possible once the outbreak is identified;
3. Maximize existing data and knowledge about the disease – by sharing it among scientists;
4. Ensure final products are available and affordable to populations in need.

1. Investing in research before the next outbreak

Research and development can be a lengthy and laborious process and years can pass before it delivers the right drug or vaccine. We should not wait for another outbreak before initiating research on lethal diseases. Due to biosafety considerations, Ebola benefited from public research in the past decade, but this early stage research was never translated into biomedical breakthroughs for at-risk populations. Despite representing more than 10% of the global disease burden, only 4% of new drugs and vaccines approved across the world were indicated for neglected diseases between 2000 and 2011. It takes vision and needs-driven priority setting to invest in R&D for neglected diseases, and such vision could save lives when outbreaks like Ebola occur. **We need to continue investing in research for Ebola, Zika, and other neglected diseases or epidemic-prone emerging pathogens.**

When incentives for innovation exist, especially if paid with public funding, they should benefit those most in need. For example, in 2007, Congress created an incentive program for research on neglected diseases called the FDA PRV program. The program works as follows: if a company, research institution or organization successfully registers a product with the FDA from a list of eligible neglected diseases, it is rewarded with a voucher, known as an FDA priority review voucher (PRV), allowing it to fast-track any other product in its portfolio through the FDA regulatory process. The voucher can also be sold to another company. The PRV program was recently improved, by lifting limits on transfers of the PRV for neglected diseases, increasing the potential appeal and value to prospective PRV recipients. The latest PRV has been sold for US$350 Million – a considerable amount of funding for R&D in the field of neglected diseases.

However, two changes must be made to ensure the FDA PRV program works as intended and for the patients it claims to support. First, the PRV program should have a **novelty requirement** to ensure it induces new investments in R&D and is not awarded to already existing drugs or vaccines. Secondly, the PRV should require **an access strategy** to ensure that patients and

treatment providers which the PRV intends to benefit will have affordable and appropriate access to products. These recommendations are a direct result from our experience in dealing with leishmaniasis, tuberculosis and malaria, where PRVs were granted for drugs that had been available in other countries for years, or from our persistent struggle to access affordable medical innovations.

2. Implementing clinical trials early in the emergency response

Prior to the EVD outbreak, MSF had never been involved in clinical trials in the midst of an emergency intervention. Yet, even though the trials were fast-tracked, relative to traditional timeframes, they started too late. When the number of Ebola-infected cases started to dwindle, as a result, trials could not be deemed conclusive.

Clinical trials pose formidable logistical, technical and ethical challenges in an emergency situation. Yet, they are feasible and accepted by local communities when all information is shared openly. With adapted and transparent trial designs in place, medical organizations could promptly experiment candidates and augment the chances of expeditiously finding new medical solutions. **MSF recommends that protocols and ethical guidelines for clinical trials during emergencies be pre-defined and agreed upon during the inter-epidemic period so when the next emergency occurs, trials can commence much sooner. The United States has, and continues to invest millions in the response and containment of epidemics. It is well placed to ensure that such mechanisms are in place to improve the response to future outbreaks**

3. Maximizing access to available knowledge

Outbreaks, be they of Zika, Ebola or influenza, are always contained through a combination of community, national and international efforts. Science is no exception to this rule; there, unity is also strength.

Collaborative research, involving timely sharing of data and specimens is being increasingly recognized as an essential means to incentivize research and leverage our understanding of diseases. Despite having learned a great deal about Ebola, many unanswered questions remain which will continue to hamper our ability to fight against the disease.

More than two years after the first case was confirmed in Guinea, responding country agencies, international organizations and NGOs involved in the response are still unable to draw a complete picture of the data, nor of the biological samples collected during the outbreak. Each of us holds a piece of the puzzle.

MSF, which has cared for more patients with Ebola than any other organization[2], has collected valuable data that we would like to share and see used ethically for research priorities by the scientific community. The CDC certainly holds the largest EVD specimen library ever collected. Nevertheless, our attempt to support the WHO in establishing networks of biobanks and data sharing platforms for EVD and emerging pathogens is poorly supported by the many actors involved – starting with the U.S. counterparts. A significant gap remains between rhetoric and action. Knowledge sharing and collaborative research are often acknowledged in principle but they face tremendous resistance when it comes to implementing them. And too often, they come too late, once the outbreak has begun.

Collaborative science should be an integral part of the culture and the response to outbreaks, with clear standards and frameworks in place beforehand to optimize the limited knowledge available. I regret to say that should another outbreak hit tomorrow, there is no ethical or organizational framework in place to ensure the collection and sharing of biospecimens or the standardization of accurately collecting routine data.

As Zika has most recently demonstrated, it is in the interest of all countries, including the United States, to guarantee a culture of knowledge and data sharing in biomedical research.

4. Ensure final products are <u>available and affordable</u> to populations in need

Innovation without access is meaningless. Improvements to the FDA PRV program to ensure medical products are made available to patients and treatment providers will be one important step toward broader changes that are urgently needed to ensure the R&D system delivers appropriate and affordable health technologies. There is an urgent need to address the global crisis of pharmaceutical companies raising drug and vaccine prices. MSF is advocating for changes in the way biomedical R&D is financed by separating cost of research and development from the price of final products.

Likewise, global quantities of available products may not be sufficient to meet all needs. There may be a need to ration them at the global level. Member States of the World Health Organization should agree on a code of conduct on stockpiling of strategic drugs and vaccines. In order to make the best and most equitable use of those products, a collective stockpiling mechanism needs to be discussed under the auspices of the WHO.

Conclusion:

Significant scientific advances are still required against Ebola and other deadly neglected diseases. Once a disease is known and starts being documented, the lack of adapted and affordable medicine is rarely unavoidable. This is often caused by our inability or unwillingness

[2] MSF Ebola Treatment Centers admitted over 5,200 confirmed Ebola cases, of which almost 2,500 have survived

to implement lessons learned and a needs-driven approach. Ebola shocked and shook the world. It gave us another opportunity to reflect on how we approach R&D.

The multiple health crises that patients are facing, including those treated by MSF, must be addressed. Every day, patients go without access to critical medical tools because such products are either not affordable, not suited to the conditions in which patients live, or simply do not exist because patients suffer from a disease not seen as a commercially attractive market.

These are challenges we have faced for decades but in 2016 several government-driven processes will take place that seek to address different aspects of the failures of the R&D system and to create global norms and efforts to deliver appropriate and affordable medical tools, including negotiations at the World Health Organization, the United Nations General Assembly and the G7/G20. This a critical and historic opportunity to make a political choice to sustain improved medical outcomes.

Being a major contributor to both the responses to global health emergencies and to research and development, the United States government can and should lead by example by boosting collaborative and open research, including but not limited to neglected diseases and emerging pathogens, ensure global investments in R&D are coordinated, target priority health needs and deliver medical tools that are available and affordable to patients and medical treatment providers by de-linking the price of drugs from their R&D cost.