The urgent need for new tools to prevent, diagnose and treat Ebola: what needs to happen

Intro

As of 7 November 2014, there have been nearly 14,000 reported cases of Ebola virus disease in West Africa and nearly 5,000 deaths. The number of new cases is thought to currently double every three weeks. The Ebola outbreak is already a major humanitarian crisis; it is likely to turn into a disaster on a much larger scale if our collective response is not radically improved.

Frontline workers, including healthcare workers in Ebola treatment centres and other health facilities, are among the most vulnerable groups of people to potentially contract the disease. More than 230 healthcare workers in West Africa have died from Ebola since the start of the outbreak. If frontline workers continue to die from the disease, the response will be difficult to sustain at the current level, let alone grow to the scale needed.

Over the last few months, MSF has voiced the need for more teams and infrastructure to control Ebola. If 70% of patients with Ebola were hospitalised in appropriate isolation rooms, then the epidemic would be reduced, some studies suggest. Recent announcements by countries, including the US, Cuba, and South Africa, among others, to deploy more human resources and build more treatment centres need to become a reality as soon as possible. More countries need to follow these examples.

In addition, new tools to diagnose, treat and prevent Ebola are urgently needed. However, given that vaccines and treatments being developed for Ebola are still experimental – and as yet unapproved for use in humans – and given that the re-purposing of drugs approved for other diseases is still clinically untested, further clinical research to prove safety and efficacy is required. There is broad agreement that research on the new tools should be conducted as a matter of priority in the affected countries, provided all international ethical standards are followed, so that any benefits are immediately derived by those most directly affected by the epidemic. The deployment of additional resources in the affected countries is therefore also a prerequisite to conduct the clinical and operational research necessary in a manner that does not disrupt, but rather supports, existing treatment and control efforts.

New diagnostics for triage, new drugs to save more lives, and new vaccines to protect frontline workers and contain the outbreak

Diagnosing Ebola virus disease currently requires a specific type of laboratory. A simple rapid diagnostic test that would not require complicated procedures or a lab infrastructure is urgently needed and would be extremely useful for triage. The test would help rule out Ebola virus disease in patients presenting with fever in health facilities and refer those suspected to be infected with Ebola to a specific Ebola treatment unit.

The mean case fatality rate of Ebola virus disease in West Africa in the current outbreak is estimated to be close to 70%, though it can be significantly reduced if the patient is treated early in an appropriate treatment unit. In addition to the current treatment, one or several specific treatments against Ebola itself are urgently required that can bring down this unacceptable mortality rate. Ideally, the treatment course would be relatively short, the drug could be administered orally (as well as by parenteral route for patients who vomit) and would have few side effects.

Most importantly, a vaccine that would give significant protection is considered a potential game-changer to reduce transmission rates and potentially help end the outbreak in West Africa. Vaccine trials should provide experimental vaccines to frontline workers as a matter of priority. Once found effective, the vaccine should be seamlessly introduced on a larger scale in the general population in areas at risk. Ideally, only one shot would be needed to give protection, and the vaccine transported in a traditional cold chain ($2^{o}C$ – $8^{o}C$) rather than requiring the vaccine to be kept frozen. The potential ability of some drugs and vaccines to prevent disease in people exposed to the virus, notably caregivers of a sick patient and other frontline workers – drugs or vaccines that could be effective as post-exposure prophylaxis tools – could also be an important factor.

Getting prepared for testing in the field

Over the last few months, many proposals of new products have been sent to MSF, WHO and other stakeholders involved in the Ebola response. A shortlist of the most advanced and promising tools has been established under the leadership of WHO. The most advanced vaccine candidates are all viral vector vaccines, while most advanced treatments are one of three different types (antibody-based therapies, RNA interference therapeutics, antivirals) [SEE TABLE]. Many of these products had never been tested in humans before the outbreak started. It usually takes nearly a decade for a drug or vaccine to go through all clinical trials in humans and reach the market. The objective now is to reduce this timeframe as much as possible and get new safe and effective products available in West Africa at large scale within the first half of 2015.

This will require an enormous amount of advance planning. MSF is currently preparing to implement clinical trials with experimental treatments as early as in December 2014. We are joining forces with research groups to adapt our sites for clinical trials; we have been continuously reviewing the landscape of pipeline products for some months; and we are selecting which products to test as a priority in the field. Our choice will be determined by the body of evidence in animal models and in healthy human volunteers, and by the assurance that the products will be accessible in sufficient quantities and affordable for all patients in need immediately after the trials have been finalised.

MSF is also in discussion with companies and other stakeholders involved in the development of new diagnostics and, most importantly, vaccines.

TABLE: list of most advanced experimental Ebola products (not exhaustive)

Viral vector-based vaccines

- ChimpAdeno3 vector vaccine
- rVSV vector vaccine
- Adeno26 vector vaccine
- MVA vector vaccine

Antibody-based therapies

- convalescent blood therapy
- hyper immune animal serum
- cocktails of monoclonal antibodies

RNA interference therapeutics

- small interfering RNA
- antisense RNA

Antivirals

- favipiravir (T-705)
- BCX-4430
- brincidofovir

Trials that maximise access

As a matter of principle, MSF will support the implementation of trials with designs that ensure that access to investigational product is maximised.

In the case of treatment for Ebola, given the high case fatality rate, MSF contends that randomised controlled trials where some patients are given a placebo are not ethical, and are likely not to be accepted by the population. During treatment trials that will be soon implemented by MSF, the investigational drug will be provided to all those enrolled in the trial. In addition, patients who are not eligible for the trial will be offered access to the drug through compassionate use whenever possible.

In the case of vaccines, there is a need to find the best compromise between the urgency to get frontline workers to access the vaccine and the need to generate solid efficacy data in a relatively short amount of time.

Market failure, public health disaster

Research for, and development of, Ebola products was long stalled, from when the virus was first discovered in 1976 until the early 2000s. Populations traditionally afflicted by Ebola virus disease did not represent a lucrative market, as the disease had affected only a limited number of people in disadvantaged areas in Central Africa.

In 2004, the US government gave a financial boost to Ebola R&D, as the virus was ranked as a major biothreat by the Department of Defense. Most Ebola pipeline products are the fruit of public funding by the US Government and few other governments, including from Canada. Unfortunately, budget cuts at the federal level in the US led to the delay or the abandonment of some critical projects.

Likewise, the licence for a vaccine developed by Canada's University of Winnipeg was given to a private company in 2010, but phase I trials are only just starting in Europe and other sites in November 2014. The lack of R&D investment to initiate and complete important studies for these vaccines, until a major outbreak occurred, are a stark reminder of why the current R&D system is fatally flawed and does not respond to many of today's public health challenges.

Collaborative and non-exclusive research and development

In order to meet the unprecedented challenge to deliver new medical tools for Ebola in just a few months, R&D efforts will require steady support and new approaches based on open collaborative research. All obstacles, except inevitable scientific and technological barriers, should be removed in order to fast track development, while ensuring that safety and effectiveness of products is properly evaluated.

In recent weeks, along with philanthropic foundations such as the Wellcome Trust, the US government has been the main supporter of the development, production and licencing of new products for Ebola. The French government has also announced the implementation of specific projects in Guinea, while Russian authorities recently claimed they would like to test and distribute in West Africa the therapeutics and vaccines they have developed in their domestic research units. These are very positive moves and MSF encourages other stakeholders to join the R&D efforts for Ebola. All initiatives should be shared with the WHO coordination team for Ebola product development, so that research teams do not overlap with one another, and develop complementary products, share common protocols and methods, and learn from each other.

Many of the products in the pipeline were initially developed by public research institutions, and then licenced to a specific company, most often a small firm. As clinical trials require a lot of technical skills and human resources, especially vaccine trials amidst an outbreak, smart partnerships may be necessary to assist small companies with investigational products. Likewise, some of the investigational products could be used in combinations, which would also require partnerships between companies. MSF urges all parties to ensure transparency for all product-related licencing agreements so that collaborative partnerships can more rapidly be established.

The scientific data generated for each product in the lab or in the field should be disclosed in real time to the international scientific community. For example, information on the series of cases treated in Europe and the US with experimental treatments has not been published in any peer-reviewed medical journal; as a result, there is a lot of speculation on the potential effects of different drugs. Preclinical and clinical data should be regularly published in open-access peer-reviewed medical journals, which are already fast-tracking review of Ebola-related papers, or on a specific Ebola web portal, placed under the responsibility of WHO.

Likewise, access to blood samples drawn from Ebola patients is of the highest importance for disease surveillance and follow-on innovation, including development of new diagnostics. Ideally, a pooled bank of samples would be established and placed under the independent authority of the World Health Organization, with approval of the Ministries of Health of countries affected by Ebola.

Scale up production now, and prioritise access to populations in need

Usually, plans to produce a new drug compound or a vaccine candidate in large quantities are not even drafted before the product has reached clinical development and, in practice, production is not ramped up until licencing has been obtained. Given the urgency to deploy new tools, we cannot afford to lose any time before production is ramped up. MSF asks developers to conduct clinical trials in parallel with scaling up production supply, so that there is no gap between the end of clinical trials and the large scale introduction of the products found to be safe and effective.

Many of the Ebola pipeline products, including some of the most promising ones, are available now only in limited quantities. For some of the products, like those involving small molecules, it will be relatively quick and cheap to ramp up production. For other more complex products based on novel technologies, scale up of production will require more efforts and significant investments in advance. MSF understands that investing now into scale up of production represents a commercial risk, as safety and effectiveness of these products are not yet demonstrated. MSF asks governments and donors to mitigate or incentivise this risk. In return, companies should be extremely transparent about the costs of goods so that donors can be reassured they will pay a price that is at or near the cost of manufacturing.

Lastly, in spite all our collective efforts, we cannot exclude a scenario where a drug or vaccine is found safe and effective, but has to be rationed because available quantities are limited. This scenario should be anticipated now and principles for equitable distribution should be established. MSF considers that distribution should be driven by needs, irrespective of where people live or the capacity of a country to pay. In practice, approved vaccines and drugs should be shipped as a priority to countries facing an outbreak or at high risk of an outbreak. Stockpiling vaccines and drugs in countries at low risk of outbreak should not be a priority. This principle is aligned with our vision that these products need to be considered as global public commodities.

What needs to happen:

MSF believes that intensified collective and collaborative efforts are critical. Several vaccine candidates and experimental treatments could be tested in West Africa as early as the end of 2014. Efficacy results could be available as early as spring/summer 2015. In an ideal scenario, a vaccine and a treatment could be introduced on a large scale in West Africa by the middle of 2015.

For this to happen, all non-scientific and non-technological obstacles should be removed, and R&D efforts should primarily respond to patients' needs:

- More isolation beds need to be created, and more human resources deployed;
- Trial designs need to maximise access, and frontline workers should be the priority group for vaccination trials;
- Local communities must be involved and informed on the process of trials to avoid misunderstanding and misperception;
- Trials should focus primarily on the products that will be accessible in sufficient quantities for populations in West Africa and which are adapted to that setting;
- Sufficient resources for clinical trials and post-trial access need to be mobilised by donors now;
- All R&D initiatives should be shared and discussed with the WHO Ebola product development coordination team;
- All product licensing agreements should be disclosed;
- Any limitations in licensing agreements which do not ensure access should be addressed by obliging manufacturers, via public funding investments and clinical trial agreements, to guarantee affordable prices to all Ebola affected patients;
- Manufacturers should agree to open licensing for an Ebola-related indication of a product;
- The scientific data generated for each product should be published in real time;
- A pooled bank of samples should be established to facilitate open research;

- Developers of front-running products need to scale up production now, in parallel of clinical trials, not after them;
- Donors need to mitigate or incentivise the commercial risk of increased production in the absence of efficacy results; and
- Principles of equitable distribution of end-products, based primarily on needs, should be established, in the event that end-products would have to be rationed.