MEETING SUMMARY OF THE WHO CONSULTATION ON POTENTIAL EBOLA THERAPIES AND VACCINES

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WHO Consultation on potential Ebola therapies and vaccines

This document is a summary of the WHO Consultation on potential Ebola therapies and vaccines held by the World Health Organization (WHO) on 4–5 September 2014 to review the pipeline of potential therapies and vaccines against Ebola and the challenges for testing and use of these in populations affected by Ebola.

Context of the Consultation

The current West African epidemic of Ebola virus disease (EVD) is unprecedented in scale and geographical distribution since the identification of Ebola in 1976. As of 5 September 2014, 3 540 cases had been reported, with an apparent overall case-fatality ratio of about 50%; many more cases have gone unrecorded. The outbreaks in some sites seem to be expanding at an exponential rate.

In the countries with epidemics – Guinea, Liberia, and Sierra Leone – many people have little or no access to healthcare, the health facilities which exist are overwhelmed, and health-care workers are themselves paying a high toll in mortality. Some of the countries experiencing major outbreaks are post-conflict States, with weak economies and infrastructure, constrained health systems, limited resources (both financial and human), and short of supplies. There are social, economic, cultural, and environmental dimensions to disease control; for example, practices around mourning and funerals carry high risks of infection. The personal protective equipment (PPE) worn by health-care workers to protect themselves from acquiring disease raises challenges regarding acceptance by the community, as well as practical difficulties from its tolerability in the heat for the prolonged periods necessary to deliver care. Concerns exist, as with outbreaks of other diseases, about risks of the appearance of counterfeit or substandard products and false claims of cures. All of these pressures influence the ability of countries and the international community to intervene effectively to terminate disease transmission.

One of the biggest challenges though, is that to date there are no known treatments or vaccines against the disease. Numerous potential therapeutics and vaccines are in development, however none have been demonstrated to be effective and none are approved for use in or against Ebola infection.

Given the urgent need to provide access to treatments and to identify which interventions are effective, WHO convened an Ethics Panel in August 2014 to provide guidance on whether these unregistered interventions should be used. The panel confirmed the ethical imperative to use and to evaluate these interventions, as long as the necessary conditions for safety, clinical care, ethical standards, data collection, and the transparent sharing of information are met, so that the most benefit and knowledge can come from their use.

Following the establishment of this ethical foundation, WHO convened this consultation in Geneva on 4-5 September 2014 to discuss with the global community the potential use of unregistered vaccines and therapies as interventions for EVD. In support of this discussion, WHO earlier convened six Expert Working Groups, which explored issues relevant to the evaluation and use of unregistered or unapproved vaccines and drugs. A distillation of their conclusions was presented at the meeting and discussed with the participants. The participants were drawn from the fields of Ebola experts and clinicians, pharmacologists and vaccinologists, pharmaceutical industry, regulators, ethicists, civil society, policy makers, and research funders, so that the approaches identified would be realistic and practical, informed by input from the range of involved sectors.

Objectives of the Consultation
The consultation focused on addressing three questions related to the unregistered products that have been proposed as being potential vaccines or treatments for EVD:

- Do these products work and are they safe?
- Can they be developed more rapidly in order that they might be moved from the laboratory to the field?
- Can they be scaled up to serve the necessary demand?

To provide a context in which to address these questions, presentations summarized the current epidemiological situation, the experiences of selected countries undergoing outbreaks or contributing to responses, how clinical case management affected outcomes, and the role of diagnosis in managing the outbreak. A summary of the product pipelines was then provided, followed by reflections on how clinical trials could be conducted, the ethical and societal issues to such trials, regulatory considerations, and practical and logistic contexts for providing care.

Country experiences
Presentations from Guinea, Nigeria, and Sierra Leone highlighted some of the major issues those countries face. These include lack of funding, reticence due to distrust of health authorities, and the belief that isolation centres are a death sentence. Rumours abound and combine with fear to cause riots and social unrest; and the burden of disease limits the ability to provide high-quality care. Speakers emphasized the need for social mobilization and culturally adapted communications, essential services, enlistment of partners, including traditional healers, and inclusion of complementary health structures in the response to the outbreaks. The need for hope in all the countries was clearly emphasized. An immediate response is vital, and, for countries not yet experiencing outbreaks preparedness is paramount. Concerns were also expressed about the potential for bioterrorism, and the introduction of fake and substandard medical products,.

Presentations from Canada, China, and Switzerland illustrated lessons learnt in their respective countries from previous epidemics of SARS and influenza and how they are preparing with domestic response plans for the possibility of EVD cases, including public health education and enhanced surveillance. They outlined their international activities in support to the outbreak, including provision of supplies and preparations for medical evacuation of foreign medical team members. Participants noted that many countries possess desperately needed assets, which could be used in response to the outbreaks. It was suggest these countries should seek ways of collaborating with the countries experiencing outbreaks.

Clinical case management
Outbreaks in capital cities and major urban centres have resulted in a high level of community exposure. The burden on the health-care delivery systems is bringing them to the verge of collapse.

Médecins Sans Frontières (MSF) is providing a large proportion of the clinical care for EVD patients in Guinea, Liberia, and Sierra Leone. Its spokesman described the grim reality it faces in the field, highlighting the very limited and basic infrastructure they are able to offer. In some centres, it is not possible to administer intravenous fluids or perform monitoring of essential indices and they can only provide beds and basic supportive care. In the tropical conditions, health-care workers can only work in their PPE for a limited time. Beds in most Ebola Treatment Units are full and demand outstrips supply as new units are opened. In addition, security is a concern and, if the population believes a ‘miracle cure’ is available, a health centre testing a product may be overrun by the population.

The scale of the outbreaks in each country pose enormous logistical problems, ranging from provision of water and electricity to recruiting safe burial teams, disposal of medical waste and transport of laboratory samples.

Good clinical care (access to doctors, intravenous fluid replacement, electrolyte balance, nutrition etc.) can significantly improve survival rates and, where feasible, this should be the base-line. Conducting clinical testing under these conditions requires careful consideration and there are a limited number of facilities where adequate infrastructure is in place to provide such care.

Diagnostics

The pressing need for diagnostics was underlined. Diagnostic laboratories are needed for surveillance, case management, and to support contact tracing. Ideally, such laboratories should be placed near treatment centres in order to reduce transport difficulties and time lags, which are currently occurring due to the limited number and distant location of the diagnostic laboratories.

Although some tests and kits are commercially available, they require full evaluation. The development of rapid, point-of-care and non-invasive diagnostic tools is urgently required. WHO's prequalification team was urged to do an Expedited Product Review to provide countries with information on the quality of these diagnostic products. Laboratory capacity, including staffing, in countries facing outbreaks must be further developed and sustained.

Participants called for the substantial strengthening of WHO's Global Outbreak Alert and Response Network (GOARN), as well as international support for strengthening of (African) national and regional networks and partners for the public health, clinical, and laboratory requirements of such a response.

Potential new therapeutics and vaccines

Multiple products are in the development pipeline, which was presented. Details of these products are available in the background document and associated annexes.

Research on these products has been conducted *in vitro* and in animal models. Of the latter, the non-human primate model is the closest to mimicking natural infection in humans. However, caution must be applied in evaluating the results of animal testing as safety and efficacy are determined by immunological, metabolic, and toxicity effects, some of which are species-specific. Differences, for instance, in immune-pathogenesis mean that products that work in animals will not necessarily prove to be efficacious or safe in humans.

Several vaccine candidates are being developed and the two most advanced vaccines identified – based on recombinant vesicular stomatitis virus expressing an Ebola virus protein (VSV-EBOV) and recombinant chimpanzee adenovirus expressing an Ebola virus protein (ChAd-EBOV) – are currently being tested in humans for safety and efficacy in the United States of America and trials will be started in Africa and Europe later in September. WHO will work with all the relevant stakeholders to accelerate their development and safe use in countries with outbreaks.

Among the various candidate therapeutics that have been identified, human convalescent plasma, whole blood, and other blood-derived therapies must receive priority consideration, as there is both theoretical and anecdotal evidence that these products can improve survival, and they will be increasingly available locally as some patients recover.

A cocktail of monoclonal antibodies against Ebola virus (Zmapp) has already been used compassionately in a few patients with Ebola, however the number is too small to enable any

assessment of safety or efficacy and it will be several months before more product is available. Other immunoglobulins, derived from immunized humans or animals may have therapeutic value. Such products, while being developed, will not be available for at least 6 months and will need to undergo testing for efficacy in non-human primates.

Other potential therapeutics under development include: novel nucleotide analogues and other small antiviral molecule agents such as favipiravir, BCX4430, brincidofovir; RNA-based drugs such as small-inhibitory RNA (siRNA) and phospho-morpholino oligonucleotides (PMOs); and drugs that affect coagulation such as recombinant nematode anti-coagulant protein or recombinant activated protein C. Some of these have demonstrated safety in humans and efficacy in animal models, however clinical evaluation will be required to determine whether they are efficacious in human Ebola infections and whether they are safe at the doses required. In addition, supplies for some of the most advanced products are limited to just a few tens or hundreds of doses.

In addition to these novel products, there are also several existing medicines that have been approved for treatment of other diseases and conditions but which may be re-purposed for EVD. These include the antiviral favipiravir, immunomodulatory drugs, such as interferons, and estrogen receptor modulators. While some efficacy has been demonstrated in small animal models with these drugs and they have a history of use in humans, it is not known if they will be safe or efficacious in EVD patients.

None of these potential therapeutics should or can replace standard care and investigation of these interventions must not distract attention from the implementation of standard clinical care, rigorous infection prevention and control, careful contact tracing and follow-up, effective risk communication, and social mobilization, all of which are crucial for ending these outbreaks. Repeated emphasis was given to the requirement of an adequate standard of care as the basis of evaluation for implementation of any of these agents.

Participants identified numerous challenges. For all these drugs, there is only suggestive preclinical evidence of efficacy. These compounds must be used in conditions where safety and efficacy can be evaluated and the relative contributions of the new therapies and standard care can be assessed. Supplies of most of these therapeutics are limited and scale-up of production will take time. The limited number of available treatment courses should be prioritized to trials which lead to evidence of efficacy. Many of these interventions require injection or intravenous perfusion – practices that impose risks to health-care workers, as well as requiring infrastructure and a sufficient number of trained staff not available at all treatment sites. Although the few oral therapies may be easier to administer, they may not be practical in patients who are vomiting or severely ill. Finally, the generation and issue of recommendations for use will depend on obtaining rigorous clinical data, which must be a priority.

Key considerations for decision makers

The choice of therapeutic agents will require continuous evaluation of data and must balance best possible care with the data on safety and efficacy. Two paths for testing new investigational therapeutics are available: clinical trials (either traditional with randomization and control arms or with adaptive design), or observational studies, including compassionate use and comparison to base-line data. Informed decisions will have to be taken about the location and capabilities of study sites, the design of clinical trials taking into account the ethics and population acceptability of any control arms, the availability of adequate product for testing, how to assess the outcomes of studies (including issues of data collection and use of endpoints), and follow-up plans for treatments assessed as beneficial including access to the product for the population.

Ethical issues

Ethical oversight is crucial, because case-fatality ratios are high, most therapeutics are still investigational, and the use of classical randomized, placebo-controlled trials may not be appropriate. The use of control groups, as well as data collection methods, and criteria for inclusion and exclusion all raise ethical issues which must be reviewed. Proposals made by participants included the establishment by WHO of a centrally coordinated, multi-stakeholder consortium for review of different interventions and for the ethical review of public health measures, consideration of gender issues, and research into culturally appropriate measures of disease control.

A plea was made that the opportunity for compassionate use be retained. This should be accompanied by work to define the requirements for data collection in compassionate use, so that the most knowledge can be gained for the future.

Regulatory issues

Regulators were recognized as the enablers who identify gaps in knowledge and the gatekeepers who protect patients by ensuring safe, effective products. Speakers highlighted the multiplicity of regulatory networks (at global and regional levels) contributing to the response and whose support could be further leveraged. It was also recognized that African regional forums and networks are taking a leading role in addressing regulatory issues. Particular reference was made to the African Vaccine Regulatory Forum (AVAREF), African Medicines Regulatory Harmonization (AMRH) programme and its pharmaceutical manufacturing plan for Africa, and the WHO-coordinated networks of regulators (including blood regulators).

National regulators in countries facing outbreaks will play a role in ensuring the quality of the research and the introduction and use of the products. Regulators in manufacturing countries will ensure conformity with Good Manufacturing Practice and the exchange of relevant data with other potential users. These networks and individual regulatory agencies facilitate design of clinical trials and use of common protocols and pooling of results, as well as access to investigational products and safeguards. Their importance in facilitating approval, testing, and regulatory pathways related to vaccines and drugs was highlighted. Countries should create simplified, functional import and export mechanisms. It was proposed that an expert group be established to develop clinical trial designs and that WHO should prepare guidance on regulatory pathways for products to be used in public health events.

Risk communications and risk management

Speakers emphasized that it is essential to identify risks in clinical trials and mitigate their impact. Communications should address perceptions about what it means to engage in studies of investigational products. It will also be essential to ensure transparency in messages and messaging. Good communication will be essential to establishing and reinforcing community trust.

Closing discussions

The lively closing discussions covered many aspects and attempted to balance the imperative for immediate action to control the outbreaks with ensuring that measures employed were appropriate, safe, and effective, in the hope that the current epidemic would be the last large-scale outbreak of EVD. It was noted that the epidemic is causing collateral damage to other disease control programmes, such as those for malaria and tuberculosis, and is interfering with peoples ability to seek and obtain other essential healthcare. Participants emphasized that the whole process must have flexible and dynamic African leadership, with WHO assuming its mandated global coordinating role. All actions must be transparent and information must be shared for maximum benefit.

Participants agreed that the highest therapeutic priority should be given to human convalescent serum, whole blood, and blood products. It was proposed that survivors of EVD should be followed up carefully, not only to determine the long-term effects of EVD, but also to identify potential donors of blood for therapeutic use. The next priority would be the promising vaccine candidates and potential therapeutics.

Participants discussed the oversight of the research agenda for evaluation and its implementation. There was consensus that this role would be best performed under the direction of WHO. Health-care and ancillary workers were felt by many to be a priority group for receiving interventions, but there are ethical considerations still to be resolved.

The need to build research capacity skills in the countries with EVD outbreaks was stressed with regard to important actions for evaluation. Proposals were made for the establishment of an international review body to review the data from the studies, an independent safety monitoring board to evaluate data from all interventions, and a register of clinical trials. WHO was encouraged to continue the work of its six Expert Working Groups and to support the development of:

- a mechanism for evaluating pre-clinical data to determine the priority of interventions to be evaluated;
- appropriate protocols for informed consent; and
- a platform for real-time collection and sharing of data.

National preparedness plans should be urgently developed by those countries which do not already have them – radically altering the "business as usual" attitude. Roadmaps should be developed with communities. Lessons could be drawn from incident-modifying interventions used in disaster responses. It was observed that patients' voices had been absent from the debate, but this omission should be rectified by their inclusion in planning. A robust plan for support of patients was required.

Participants underlined that the choice of the approaches or interventions to implement had to be predicated on a multidisciplinary effort. Support was expressed for urgent investment of effort into the development of rapid and near-patient diagnostic tests. Proposals were made for the establishment of research centres in each of the affected countries. It was also stressed that research involve the community and that it must address behavioural aspects. And further, that EVD and its implications be considered when identifying national development goals.

Stress was put on leadership, prioritization, and coordination. By November 2014, initial data will be available from vaccine Phase I safety trials. Meanwhile, countries should make an inventory of their health-care workers in preparation for planning the introduction of vaccines.

Conclusions

There are already existing supportive medical interventions that may improve the outcome of EVD. The priority should be to make certain that those interventions to ensure adequate standards of supportive care will be implemented as routine. New and unregistered interventions can best be assessed if this essential supportive care is already in place. Countries should not wait for the arrival of novel therapies, but instead should focus on assuring basic supportive care throughout their health-care delivery systems.

Response should be national and regional, with support from the wider international community. Through the evaluation of new interventions, the response can provide hope that another such devastating outbreak will not recur.