POTENTIAL EBOLA THERAPIES AND VACCINES

THIS DOCUMENT BUILDS ON A BACKGROUND PAPER PREPARED FOR THE 4-5 SEPTEMBER 2014 WHO CONSULTATION ON POTENTIAL EBOLA THERAPIES AND VACCINES AND INCLUDES INFORMATION GATHERED AT AND FOLLOWING THIS CONSULTATION

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ABBREVIATIONS

AE	adverse events
AVAREF	African Vaccine Regulatory Forum
BRN	Blood Regulators Network
ChimpAd3 / cAd3	chimpanzee adenovirus serotype 3
CRF	case record form
EBOV	Ebola vaccine
EMA	European Medicines Agency
EVD	Ebola virus disease
FDA	Food and Drug Administration (United States)
GMP	Good Manufacturing Practices
HBV	hepatitis B virus
HCW	health-care workers
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICG	International Coordinating Group (for Yellow Fever vaccines)
IHR	International Health Regulations
IM	intramuscular
IPC	infection prevention and control
ISARIC	International Severe Acute Respiratory and Emerging Infection Consortium
IV	intravenous
IVIG	intravenous immunoglobulin
LNP	lipid nanoparticle
MARV	Marburg virus
MCM	medical counter measures
MSF	Médecins Sans Frontières
NHP	non human primates
NIH	National Institutes of Health (United States)
PEGASYS	Peginterferon alfa-2a
PI	post infection
PK	pharmacokinetics
Potential	Yet unproven, unregistered against Ebola, experimental
RIG	rabies immunoglobulin
RSV	respiratory syncytial virus
rVSV	recombinant vesicular stomatitis virus
SAD	single ascending dose
SAE	serious adverse event
SE	severe event
SQ	subcutaneous
TIG	tetanus immunoglobulin
WHO	World Health Organization

BACKGROUND

Introduction

The 2014 Ebola virus disease (EVD) outbreak continues to evolve, creating challenges for the many international partners providing support. Three affected countries — Guinea, Liberia, and Sierra Leone — struggle to control the infection against a backdrop of severely compromised health systems, significant deficits in capacity, and fear.

WHO estimates that six to nine months will be needed to control the outbreak and has released an Ebola Response Roadmap detailing what needs to be done to achieve this.[1]

Recent intense media coverage of experimental medicines and vaccines is creating some unrealistic expectations, especially in an emotional climate of intense fear. The public needs to understand that these medical products are under investigation. They have not yet been tested in humans and are not approved by regulatory authorities, beyond use for compassionate care.

Evidence of their effectiveness is suggestive, but not based on solid scientific data from clinical trials. Safety is also unknown, raising the possibility of adverse side effects when administered to humans. For most, administration is difficult and demanding.

Safe administration of some potential interventions requires facilities for intensive care, which are rare in West Africa. WHO has advised that the use of experimental medicines and vaccines under the exceptional circumstances of this outbreak is ethically acceptable (summary of recommendation from Ethics Panel, 11 August 2014).[2] However, existing supplies of all experimental medicines are either extremely limited or exhausted.

While many efforts are under way to accelerate production, supplies will not be augmented for several months to come. This is especially true for therapies, where expected supplies are not thought likely to have a significant immediate impact on the outbreak. The prospects of having augmented supplies of vaccines quickly look slightly better.

Therefore, it should be noted that the potential compassionate use and further investigation of these compounds should not detract attention to the implementation of effective clinical care, rigorous standards of practice in infection prevention and control (IPC), careful contact tracing and follow-up, effective risk communication, and social mobilization, which will be crucial to terminate the epidemic.

On 4–5 September 2014, WHO held a Consultation on potential Ebola therapies and vaccines. The Consultation was convened to gather expertise about the most promising experimental therapies and vaccines and to consider their contribution in containing the Ebola outbreak in West Africa.

Issues of safety and efficacy were discussed together with innovative models for expediting clinical trials. Possible ways to ramp up production of the most promising products were also explored. Presentations about the real conditions and challenges in affected African countries informed the discussions during the consultation.

[1] Ebola Response Roadmap. WHO/EVD/Roadmap/14.1. Geneva: World Health Organization, 28 August 2014. Available at: http://apps.who.int/iris/bitstream/10665/131596/1/EbolaResponseRoadmap.pdf.

[2] Ethical considerations for use of unregistered interventions for Ebola virus disease. Report of an advisory panel to WHO. (WHO/HIS/KER/GHE.14.1.) Geneva: World Health Organization, 2014. Available at: http://who.int/csr/resources/publications/ebola/ethical-considerations/en/.

Objectives of this document

The aim of this background document is to assist Member States and relevant partners in their discussions to identify the best approaches to ensure the accelerated evaluation and use of available or near-term therapies and vaccines for the treatment and prevention of EVD. The document calls for a coordinated effort by the international community to remove unnecessary obstacles towards this goal.

This document builds on current knowledge and available information on potential therapies and vaccines. It has benefitted from the contributions from the members of six *ad-hoc* Working Groups (Annex 1) who supported the WHO Secretariat in the preparatory work for the Consultation.

Intended audience

This document builds on the Background document prepared for the September 4-5, 2014 Consultation. It includes proposed elements to consider during the development of a framework to assist decision-making at global and national level.

This document has been revised for broader dissemination to include information and perspectives gathered during the Consultation. This revised version is intended for senior government and partner agencies officials responsible for proposing country-level actions.

Key questions

Box 1. Three key questions were proposed to initiate the discussions on assessment and use of experimental therapies and vaccines

1. What should be the overall OBJECTIVES of a plan for evaluation and use of unregistered interventions (therapies and vaccines) as a response to the current outbreak and in preparation for the future?

- Which principles should guide the development of such objectives?

2. What are the most important ACTIONS to ensure successful evaluation and use (if appropriate) of any of these investigational interventions (therapies and vaccines)?

- What are the existing assets?
- What are the anticipated challenges?
- What actions are required at global and national levels (in the short term and in the long-term)?

3. What kind of SUPPORT is required to ensure successful implementation of proposed plans for the evaluation and use of interventions (therapies and vaccines)?

What are the opportunities and required resources to strengthen capacity (for research, ethical, and regulatory oversight) in Africa?

- What is the role of the national authorities?
- What is the role of the international community?
- What financial resources are required in the short and long term to ensure a healthy therapeutics and vaccine pipeline and the availability of safe and effective interventions?

1. EBOLA THERAPIES AND VACCINES: WHAT'S IN THE PIPELINE?

The following table lists potential therapies and vaccines for EVD and provides information about how the interventions might work. It also summarizes the research that has been conducted, what is known about safety and availability, and the feasibility of use under current conditions. The list has been produced after a review of studies exploring the effects of potential therapies and vaccines *in vitro* and in animal models and following discussions with clinicians and virologists conducted by WHO and its partners from the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC).[3]

1.1 Lead experimental therapies

Table 1. Overview of scientific information on potential therapies under development (Annex 2)

Therapy	What it does?/ State of research	Safety	Availability/feasibility
Convalescent plasma	Studies suggest blood transfusions from EVD survivors might prevent or treat Ebola virus infection in others, but the results of the studies are still difficult to interpret. It is not known whether antibodies in the plasma of survivors are sufficient to treat or prevent the disease. More research is needed.	Safe if provided by well-managed blood banks. Risks are like those associated with the use of any blood products, such as the transmission of blood-borne pathogens that cause disease. There is a theoretical concern about antibody-dependent enhancement of EVD infection, which can increase infectivity in the cells.	Blood transfusion is culturally acceptable in West Africa. Potential donors are Ebola survivors, but the logistics of blood collection are an issue. Options to conduct studies in patients are being explored. The first batches of convalescent plasma might be available by the end of 2014.
ZMapp Cocktail of three chimeric mouse-human monoclonal antibodies (Mapp Biopharmaceutical Inc.)	The three antibodies in this mixture block or neutralize the virus by binding to or coating a different site on the covering or "envelope" of the virus. Studies in non human primates (NHPs) showed a strong survival up to five days after infection, when virus and/or fever were present.	There have been no formal safety studies in humans. Very small numbers of EVD-infected people have been given ZMapp on a compassionate basis and no safety issues have been reported to date. Clinical effectiveness is still uncertain.	A very limited supply (fewer than 10 treatment courses) has been deployed to the field. At the date of publication of this revised document no doses remain. Efforts to scale up production may yield increased supplies of potentially few hundred doses by the end of 2014.
Hyperimmune globulin prepared by purifying and concentrating plasma of immunized animals or previously infected humans with high titres of neutralizing antibody against EVD	Antibodies that can neutralize the different EVD strains have been produced and shown to be protective in NHPs when treatment begins 48 hours after exposure to EVD.	Generally safe. There has been extensive experience with the use of hyperimmune globulin against other infectious agents in humans. Inactivation and purification procedures effectively eliminate blood-borne pathogens that cause disease.	Not currently available. Several months are needed to immunize animals, collect plasma, and make the purified product. Work is starting on the production of immune globulin in horses and of human immune globulin in cattle. Studies in horses could take place within six months, but large-scale batches for use in humans are not expected before mid-2015.
TKM-100802 Lipid nanoparticle small interfering Ribonucleic acid (siRNA)	These target two essential viral genes to stop the virus from replicating. Effective in guinea pigs and monkeys. In NHPs, there is an 83% survival rate, if	A single-dose study in healthy volunteers found side effects include headache, dizziness, chest tightness, and increased heart rate at high doses. At	The US Food and Drug Administration (FDA) has authorized emergency use in EVD-infected patients and several such patients have

[3] This document is adapted from POTENTIAL MEDICAL INTERVENTIONS FOR EBOLA: Clinical decision-making support tool for investigational therapeutics for Ebola virus infection (Interim version 6.2 of 10 August 2014), WHO and ISARIC.

Therapy	What it does?/ State of research	Safety	Availability/feasibility
(Tekmira)	administered 48 hours after infection and 67% survival 72 hours after infection.	lower doses, projected to be the dose used for treatment, the drug was better tolerated.	received treatment with this product. A limited number of treatment courses (15-20) are available. There is potential for the production of up to 900 courses by early 2015.
AVI 7537 (Sarepta) Phosphoro-diamidate oligonucleotide	In NHP studies, doses of 14 to 40 mg/kg for 14 days showed typical survival ranging from 60% to 80% when given at the time of infection.	Human tolerability has been demonstrated in early studies.	The active pharmaceutical ingredient is available for 20-25 courses by mid-October 2014. Potential production of approximately 100 treatment courses by early 2015.
Favipivavir/T-705 (Toyama Chemical/Fuji Film)	This has shown effectiveness against EVD in mice, but in a NHP study only one out of six survived. Another study of animals using a different dose regimen is underway.	Approved in Japan for influenza treatment under special circumstances. Remains under study in other countries. Has been tested in more than 1 000 people, with no major adverse effects reported. But the dose proposed for treatment of EVD could be 2-5 times higher than that tested so far and duration of treatment might be longer than in current influenza studies. It should not be used during pregnancy due to potential birth defects. It has not been studied in humans for Ebola.	Use for field post-exposure prophylaxis is under discussion. More than 10 000 treatment courses may be available, pending determination of the dose for treatment of EVD. Future supply is not limited.
BCX4430 (Biocryst)	Studies of this antiviral in animals indicate 83% to 100% survival in rodents with EVD. It is also effective in animals 48 hours after infection with the lethal Marburg virus, which belongs to the same family as Ebola. Testing for EVD in NHPs is underway.	No human safety studies or data available. Safety studies are planned.	Needs NHP protection data for EVD before it can be considered. No material is currently available for field use.
Interferons	Induces an antiviral state in exposed cells and regulates the immune system. A study showed delayed time to death in NHPs but no overall increased survival. Early administration enhances the effectiveness of treatment in animals and lengthens the time after the viral infection at which antibodies show effectiveness.	Various forms approved for treating chronic hepatitis and multiple sclerosis. Higher doses are associated with increased adverse effects but no greater efficacy.	Commercially available. There are several types of interferons. Decisions regarding which one to use, when to use, and the dose regimen need careful consideration.

1.2 Vaccines under development

A number of candidate EVD vaccines have been tested in animals, but most are not available in formulations suitable for human use.

Two promising candidate vaccines (GlaxoSmithKline and NewLink) have been tested in animals and are now being tested in Phase 1 human clinical trials to determine whether they are safe and induce immune responses. One vaccine was given to a laboratory worker several years ago after exposure to EVD in a laboratory.

Both vaccines are recombinant, meaning that a different virus (expected to be safe in humans) causes the expression of just one component of EVD within the vaccinated human in order to stimulate immunity to Ebola virus without risk of causing disease itself.

The goal is to induce effective immune responses and protection from subsequent infection. In the first human trials, safety and immune responses will be determined in a small number of volunteers.

A third vaccine (Johnson & Johnson) has shown promise in nonhuman primate (NHP) challenge studies, and a Phase 1 clinical trial is planned to start in January 2015.

Other vaccines are in development (VSV-Profectus; purified GP-Protein Sciences; DNA-Inovio; 3 candidate vaccines-Russian Federation) and NHP studies are also expected in the months ahead.

Table 2. Overview of scientific information on vaccines under development (Annex 3)

Type of vaccine	What it does/state of research	Safety in humans	Availability
Chimpanzee adenovirus serotype 3 (ChAd3) vaccine	Uses a chimpanzee adenovirus that does not grow, containing the gene for EVD surface protein. A single dose of the vaccine given one month in advance protected 16/16 animals from a lethal dose of EVD.	More than 1 300 people have received similar vaccines for other diseases, including over 1 000 people in Burkina Faso, Gambia, Kenya, and Senegal. These other vaccines seem safe so far, but as yet there is no safety information on an EVD vaccine in humans.	There is no information from human trials. An early trial of an EVD vaccine containing two EVD strains, Zaire and Sudan, started in September 2014 in the United States of America (USA). A vaccine against Zaire EVD may be evaluated in the United Kingdom (UK), and then in one or two African countries starting in October 2014. The earliest availability depends on results of trials and manufacturing timelines. Approximately 15 000 doses might be available by the end of 2014.
Recombinant vesicular stomatitis virus (rVSV) vaccine	The rVSV vaccine aims to induce EVD-specific immune responses. A single dose of the vaccine given one month in advance protected 16/16 animals from a lethal dose of EVD. Animals with weakened immunity were not harmed by rVSV-EVD. The vaccine was safe when injected directly into the brain of animals.	It is unknown if rVSV-EVD will grow in humans, especially in people with weak immunity. Too little growth could make a weak vaccine, while too much could cause illness or possibly spread to unvaccinated people or animals. One laboratory worker was given rVSV after a needle stick injury and remained well. This does not prove the vaccine will be safe or protective. The laboratory worker had a small but detectable amount of vaccine in plasma for a short time after rVSV-EVD vaccine injection.	Safety, efficacy, and duration of protection are unknown. A trial is due to start soon in the US. Currently, 800 doses are available and more is in production.

The products in Table 2 were prioritized for consideration based on the availability of NHP efficacy data with a filovirus challenge and justification for a human dose based on clinical data of the product or comparable products within that class.

The lists provided in Tables 1 and 2 were prepared based on data available to WHO as of 10 August 2014. Since the publication of this document in draft form on 4 September 2014, information on numerous other products has been received, including: antivirals; molecules that can modify the immune response to the virus; factors that modulate clotting; and other vaccines. For some of these products, human safety data is available as well as limited data on efficacy in preclinical models. WHO has also received proposals for experimental interventions for which there is no scientific justification or supportive data. The Working Group that was established to review potential therapeutic interventions is reviewing all of these and updated prioritization will be published in real-time based on available information.

One antiviral (brincidofovir) not included in the above list, but for which extensive human safety data at the dose thought to be effective against Ebola is available, has been identified by the Working Group for prioritization. This drug cannot readily be tested in NHPs due to pharmacokinetic differences with humans, therefore alternative proof-of-concept models are being explored.

2. DEVELOPING ACCELERATED PATHWAYS FOR LICENSURE

2.1 Major ethical and regulatory issues for consideration

The unproven Ebola therapies and vaccines under consideration are at early investigational stages of development. They have not yet been evaluated for safety or efficacy in human trials for the treatment or prevention of Ebola virus disease (EVD). Moreover, supplies for some investigational products are extremely limited.

Harmonizing ethics review and improving communication

Development of candidate drugs and vaccines is a concerted effort of multiple institutions based in different countries. Ethics committees from the participating countries are required by regulation to review and approve the research protocols. Flexible approaches are required to harmonize these various review processes and ethics committees must be willing to review the projects simultaneously and share and discuss the review outcomes with each other. Early discussions with the drug regulatory authorities are helpful in facilitating timely approval of clinical trials. In addition to the usual risk benefit assessments carried out by ethics committees, they also have the responsibility of ensuring that communities have been properly engaged in pre-trial discussions and are informed about the risk benefit assessment in terms that they can understand. Such prior engagement and effective communication can go a long way in community acceptance and success of trials.

In some countries in the African region, ethics committees do not have the necessary expertise to review clinical trials, therefore WHO will facilitate twinning mechanisms with other African countries which have the necessary expertise, in addition to supporting long term development of ethics capacity. A WHO international ethics advisory group is available to provide advice upon request to the various groups on emerging ethical issues.

Accelerating development, regulatory assessment, and product licensing

Accelerating the development of experimental/not approved EVD therapies and vaccines requires a concerted effort by product developers and regulatory agencies in cooperation with the WHO. Decisions on which products are advanced for accelerated development should be transparent and involve all stakeholders, including the countries that are affected. Interactive, flexible, and expedited but rigorous review processes are needed. While there is an urgent need for product to be used on a compassionate basis, the ultimate goal should be product approval so that countries affected by EVD have products at their disposal which have been demonstrated to be safe and effective for use in both the current epidemic and any EVD future outbreaks. Early use mechanisms for investigational products should allow for the collection of interpretable data that informs product development and ultimate approval.

Regulatory authorities should consider the most efficient paths to bring these products to registration. They should share information about regulatory approaches and, to the extent possible, develop harmonized data requirements. Regulators from affected countries should be directly involved in discussions with regulators from countries where the products are being developed. The benefit-risk assessment will differ depending on the category of product; therapeutic products, which will be given to sick patients, will have a different threshold of acceptance than prophylactic products, which will be given to healthy persons. Good Manufacturing Practice (GMP) compliance is expected for product approval and appropriately adapted for clinical trials. It is important to provide assurance of quality and consistency of batches. Changes during the development of an investigational product must be properly controlled, evaluated, justified, and documented.

Facilitating access to investigational products

It is critical to balance the need for rapid access to investigational products with the need to gather data on the safety and efficacy of the products. Therefore, use of clinical trials to evaluate and provide access to these products is recommended over purely compassionate use mechanisms, when possible. The use of clinical trials better supports advancement of product knowledge and ensures appropriate controls are in place for patient safety and collection of data to support product assessment. A randomized study should be done where feasible, because of the strength of the data generated. However, when blinded, placebo-controlled or no-added-treatment-controlled trials are not possible, sequential enrolment of EVD patients into open-label studies that prospectively collect standardized clinical and laboratory data can provide evidence for analysis. Common clinical trial protocols, ideally with a simple design, should be used if products are tested across more than one site and country to facilitate pooling of results. Any regulatory approach for early access should provide adequate safeguards for the patients (i.e., informed consent, safety monitoring) while enabling accelerated access to potentially lifesaving interventions. Simple informed consent forms have been developed and can be modified for specific products.[4]

Network of Regulators

Data on the safety and efficacy of candidate products should be shared as soon as possible with the regulatory community. Regulators should agree to work together to pool and analyse results from studies. A network of regulators will be established by WHO and should also link with existing networks, such as the African Vaccine Regulatory Forum (AVAREF). The network will share information as it becomes available, establish minimum data requirements for compassionate use and product approval, and support other regulators. Technical assistance could also be offered on a bilateral basis to provide support to countries conducting clinical trials (e.g., an affected country involved in clinical trials and a country where product originates).

Import/export requirements

Countries should review their import and export requirements, especially as they pertain to clinical trial materials to ensure this does not become an obstacle to accelerated development and/or compassionate use. Existing guidance, for example from AVAREF[5], on import/export issues may be helpful.

2.2 Potential study designs for evaluation

Highly pragmatic, simple designs are needed to accommodate the particular issues inherent in this Ebola epidemic, including safety, personnel, and other resource limitations of participating facilities.

The study design should address the imperative of essential clinical care delivery. If an experimental intervention is given by random allocation, all patients in a trial should receive the best available standard of care. The study design should also attempt to minimize bias in evaluating the causal effect of the intervention.

Limited information will make planning an intervention study difficult. For example, how can the very limited information available from different Ebola Treatment Centres on observed case fatality rates be used to calculate sample sizes for trials of therapeutics.

Similarly, information on incidence of infection among different risk groups is necessary to calculate sample sizes for a vaccine trial.

[4] Informed consent form templates are available at http://www.who.int/rpc/research_ethics/informed_consent/en/.
[5] African Vaccine Regulatory Forum Guidelines for regulation of vaccine clinical trials, 2010.

A single data monitoring oversight committee should have real-time access to all data. The study design should allow data to be evaluated in real time to permit the adaptation of interventions as data becomes available.

All contributors should collect a unified core data set. Collection of such data from both randomized control trials (RCTs) and observational studies would provide needed information about prognosis and prognostic factors that will help to determine sample requirements for planned future trials. When RCTs are not possible, data from historical controls or from patients not enrolled in formal studies could be analysed. Both the data sharing and the analysis should occur in real time, so that the information can be rapidly used to adjust actions.

Box 2. Considerations on potential study designs to obtain additional scientific evidence on effectiveness and safety

The study design should minimize bias in evaluating the causal effect of the intervention. This must be balanced against demand for treatment, equity, and other ethical considerations.

- Case reports, case series: provides valuable information from those receiving the interventions. Without concurrent control group the validity for efficacy evaluation is limited unless a dramatic effect is observed.
- Carefully designed observational studies, with defined, standardized data collection protocols, comparing outcomes in patients who have received an intervention with patients in an historical or concurrent control group: interpretation of an observed difference (or lack of difference) in outcomes is difficult.
- Randomized, placebo-controlled trials may not be considered ethically acceptable. Randomization to two different experimental therapies may be more acceptable. Those unwilling to be randomized can be followed as a control group receiving usual care to improve the generalizability of study results. This would demand true equipoise about the comparative value of the two treatments offered in relation to each other and to standard care.
- Level of randomization or other allocation method: individual vs. cluster.
- Adaptive randomized clinical trials design can be useful to evaluate multiple arms of treatments and different subgroups.
- Considerations regarding the differences in potential study designs for therapies and vaccines and between therapeutic and prophylactic interventions are important.

2.3 On-going or planned studies

International consortia have been formed in collaboration with WHO to expedite high quality, ethical clinical trials to assess safety, and in the case of vaccines, immunogenicity of experimental Ebola interventions.

Networks set up in August 2014 plan vaccine clinical trials in the European Union (EU), UK, the US, and several locations in Africa. In the US, UK and Mali, clinical trials were begun in September and trials are due to start in late October-early November in the EU (Germany and Switzerland), Gabon and Kenya. Phase 3 efficacy trial will start in December 2014-January 2015.

Activities are also ongoing to facilitate interactions between regulatory agencies and ethics committees to support expedited clinical trials. The WHO-coordinated AVAREF will support African regulatory agencies and ethics committees in assessment of clinical trial applications with support from the European Medicines Agency (EMA) the Public Health Agency of Canada (PHAC), and the US Food and Drug Administration (FDA).

Information and preliminary timeliness on the current plans for assessment for potential therapies and vaccines are in Annexes 2 and 3.

3. EVALUATION AND EMERGENCY/COMPASSIONATE USE OF UNPROVEN INTERVENTIONS

3.1 Objectives of the plan for emergency use and assessment (if appropriate) of unproven interventions

Considerations

- Beyond the immeasurable value of saving lives, actions can be designed so that the lead experimental therapies and vaccines can be used promptly and in a way which could contribute to their future licensure.
- Political and logistical considerations, along with issues regarding community acceptance and the need to manage expectations, have been highlighted by the recent and publicized access to experimental treatments provided to a few Ebola patients.
- Defining objectives will be an on-going process, influenced by factors such as the evolution and spread of the outbreak and the emerging evidence on the safety and efficacy (or lack thereof) of unproven interventions.

Box 3. Potential objectives, by perspective, used during the Consultation to inform deliberations on the use and assessment of unproven therapies and vaccines

Individual perspective

- Imperative to rescue individuals facing "potentially avoidable" death.
- To avoid or minimize harm as most therapies and vaccines have very limited safety information available.

Public health perspective

- To develop an approach to identify key individuals/populations to be targeted (e.g. role in outbreak response,[6] potential for intervention to be efficacious among this population, other).
- To consider the likelihood of obtaining additional critical safety and efficacy information.
- Impact on communities´ trust in public health interventions.

3.2 Proposed criteria for assessing the likely value of the compassionate use / assessment of lead experimental therapies and vaccines

Some basic criteria *("reality checks")* are suggested to guide deliberations on readiness for use (Table 4).

These include: minimal scientific data desirable (minimum data that can be used as a reasonable predictor of safety and/or efficacy); current status of development (highest level of scientific data available); "trigger and or a priori define milestone" to move from scientific evaluation to emergency/"compassionate" use; availability in the short term (current major limiting steps); and anticipated outcomes of a "benefits and risks assessment".

[6] Treating HCWs will help them care for others. Reciprocity: in turn for their risking their lives

Table 4. Summary of unproven therapies and vaccines according to proposed criteria to guide deliberations on evaluation and use

Type of intervention	**Minimal scientific data desirable** *(minimum data that can be used as a reasonable predictor of safety and/or efficacy)*	**Current status (August 2014) Highest level of scientific data available**	***"Trigger/ milestone"*** **(to move from scientific evaluation to emergency/"compassionate" use)**	**Availability short term/ Current major limiting steps**	**Anticipated "benefits and risks assessment" process** [e.g. Definitely consider; possibly consider; do not consider]
Therapies					
Immunoglobulins *(1) Convalescent plasma* *(2) Hyperimmune globulin* *(3) Monoclonal Abs*	Human safety; for hyperimmune and monoclonal antibodies: effective in NHPs	(1) Uncontrolled data in humans (blood transfusions); convalescent Ig monkey preps protected NHPs (2) evidence of effectiveness in NHPs, extensive experience with other hyperimmune globulins; generally safe; (3) strong therapeutic effect in NHPs; no phase 1 human safety, PK data	Risk from disease should outweigh potential risk from treatment; life-threatening disease; no alternative treatment is available; risks not unreasonable in context of disease	(1) Theoretically feasible to recruit large numbers of EVD survivors to collect plasma; need appropriate screening, processing, plasma-pheresis infrastructure; safe blood collection; no BRN collaborating centres in West Africa (2) No hyperimmune globulin available before mid-2015 (3) current supplies reportedly exhausted; limited production capacity	(1) Consider if limiting factors can be addressed and safe collection and production ensured (2) Consider pending ability to produce sufficient quantity, NHP data, and appropriate storage can be assured (3) Already in compassionate use: use experimentally (collect data) if production can be scaled-up
Immunomodulators and antiviral drugs *(1) Interferons* *(2) Favipiravir/T-705* *(3) BCX4430*	(1) Effective in NHPs; (2) Effective in NHPs and safety/ tolerability of higher doses;	(1) No increase in survival in NHPs; extensive experience with other diseases; (2) Only 1/6 NHP protected in initial study; NIH repeating with higher dosage; benefit observed in murine model; approved for treating certain influenza in Japan; no significant safety concerns, but contraindicated in		(1) Commercially available, require experienced clinicians to administer; (2) Tolerability of higher doses; appropriate dose for EVD unknown; contraindicated in pregnancy (how to determine?); >10,000 doses available;	(1) Benefit: risk unknown; potential SAEs – use with caution by physician able to monitor and treat AEs. (2) Higher doses than currently approved thought to be required: wait for NHP data and use with caution in conditions where data on safety and efficacy can be evaluated.

	(3) NHP benefit, safety in humans	pregnancy; the vast majority has no paediatric data (3) benefit in mice and guinea pigs; NHP studies in progress; no human safety		(3) no human safety or PK data; none available for use	(3) Do not consider until data showing protection in NHPs and safety in humans are available
Type of intervention	**Minimal scientific data desirable** ***(minimum data that can be used as a reasonable predictor of safety and/or efficacy)***	**Current status (August 2014) Highest level of scientific data available**	***"Trigger/ milestone"*** **(to move from scientific evaluation to emergency/"compassionate" use)**	**Availability short term/Current major limiting steps**	**Anticipated "benefits and risks-assessment" process** [e.g. Definitely consider; possibly consider; do not consider]
siRNAs *(1) TKM 100802* *(2) AVI 7537*	(1) safety data (2) PK and tolerability data; inhibition v. current EVD OB strain	(1) Strong in vitro activity; effective in NHPs, 7d better than 4 days; dose-related transient tolerable SE (2) 62% survival against EVD in rhesus macaques; no safety concerns in Phase 1 SAD (IV admin x 2 weeks)	(1) FDA has authorized emergency use in infected patients and as post-exposure prophylaxis.	(1) Dose-related SE; lower dose better tolerated (modelling indicates 2.4 mg/kg dose should be effective); study in healthy volunteers on hold; very limited availability – could possibly expand to 900 courses by early 2015; (2) active ingredients available for 20-25 treatment courses; need to be formulated	(1 and 2) Consider for treatment of infected patients (authorized by FDA for (1)). Prioritize diagnostically confirmed cases due to limited supply. Use early in infection if possible.
Vaccines					
Chimpanzee Adenovirus Serotype 3 (ChAd3)	Safety of Ebola vaccine in humans – Phase I data	Protected 100% of 16 NHPs; ChAd3 carrying proteins against HCV and RSV has been tested in 290 persons, and against malaria in 1000; no serious safety concerns	Will results from Phase I trials provide the required scientific information?	Need safety data from an expedited Phase I trial; consider monovalent Zaire EVD vaccine which may be more immunogenic at lower doses than bivalent Zaire+Sudan; monovalent available but needs to finish and fill; could be available by late 2014 (15,000 doses) pending investment to scale-up	Definitely consider in high-risk groups pending Phase I trial safety results.

Recombinant vesticular stomatitis virus (rVSV)	Human safety data – unknown if virus replicates and could lead to onward transmission and could be of concern in immunodeficient individuals	Tested in 20 NHP with 100% protection. Safe in immune-compromised rhesus macaques; evidence of protection in rodents and NHPs; 80 US adults enrolled in rVSV-HIV vaccine Phase I trial – no published results.	Will results from Phase I trials provide the required scientific information?	No human safety data; 800 doses available, donated to WHO	Consider pending human safety data

(Numbers in parentheses refer to terms in left column, all across the row [e.g., (1) refers to "convalescent plasma" in first row, to "interferons" in second, etc.])

3.3 Major regulatory considerations for emergency/compassionate use

Regulators will need to propose what level of information is needed on the quality and non-clinical testing of the products prior to compassionate use.

Moreover, investigational therapeutics generally need to be administered in a setting that can provide supportive care. Establishing the capacity to provide basic supportive care (e.g., administration of fluids and electrolyte replacement) as an initial step towards facilitating access to investigational therapies could provide significant health benefits to patients in affected areas.

Minimum data requirements could be established for product approval, taking into account product-specific considerations. Existing regulatory pathways could be considered in this exercise (e.g., US Animal Rule, Canadian Extraordinary Use New Drug Regulations).

3.4 Major ethical issues for consideration in the context of emergency/ compassionate use

Ethical considerations are central to the decision-making about the use of potential interventions, both at the individual and public health levels. Here are key principles to take into account:

- Individual ethical principles: beneficence, non-maleficence, distributive justice, respect for autonomy;
- Public health theories and values: egalitarianism,[7] utilitarianism,[8] deontology,[9] human rights;
- Public health principles: fairness, effectiveness, interdependence, solidarity, procedural justice (transparency, accountability, participation), scientific evidence.

Use of experimental interventions

In the context of this unprecedented Ebola virus disease outbreak, and the lack of approved treatments or vaccines, a WHO Ethics advisory panel met on 11 August 2014 and recommended that it is ethically acceptable to offer experimental interventions that have shown promising results in the laboratory and in relevant animal models to patients and people at high risk of developing the disease, with the proviso that certain conditions are met. In spite of the novel circumstances posed by the Ebola outbreak, internationally agreed standards of research ethics and human rights must apply. Approval from recognized local research ethics boards is required prior to the use of any investigational agent, and informed consent of individuals receiving investigational agents should be obtained.[10]

Fair allocation of interventions

At least initially, only very limited quantities of the interventions will be available. Policy-makers will face hard choices about how to prioritize these scarce resources and will have to base their decisions on an ethically and publicly defensible set of criteria. Given the moral and empirical complexities of the current situation, it is unlikely that any one single ethical principle or consideration will be sufficient alone to establish an ethically acceptable and pragmatically sound policy. The potential for

[7] Ethical doctrine, defined as the belief that everyone should have equal economic, political, and social rights.
[8] Ethical doctrine, it is a belief suggesting that an action is morally right if the majority of the people benefit from it.
[9] Ethical doctrine, which holds that the worth of an action is determined by its conformity to a binding rule rather than by its consequences.
[10] Ethical consideration for use of unregistered interventions for Ebola virus disease: Report of an advisory panel to WHO. Geneva, World Health Organization, 2014. Available at http://who.int/csr/resources/publications/ebola/ethical-considerations/en/.

conflict between individual and public health values and principles should be anticipated. This is why a fair, inclusive, transparent process of decision-making is paramount for reaching acceptable solutions. Hence, the goal is to seek reasonable consensus in the context of a fair deliberation and to consider in advance ways to manage principled disagreement among affected parties and stakeholders. The detailed advice of this group is provided in Annex 4.

Rights and obligations of health-care workers

Health-care workers engaged in supportive care for patients with EVD and in the evaluation of these vaccine and therapeutic agents have rights to health and a safe workplace. Issues of professional ethics, including the scope of the duty to care and whether there is an obligation among health-care providers to be engaged in evaluative activities that may increase risks to their health over and above the current significant risks entailed by caring for patients with EVD need to be weighed. Informed consent of individuals receiving investigational agents and consent of health-care providers to be involved in their evaluation must be secured.

Table 5 provides an overview of some of the potential beneficiary populations and some proposed decision-making criteria that could facilitate deliberations of who and when and under which circumstances individuals may be considered for participation.

Table 5.Potential beneficiary populations and elements to guide the deliberations on participation

Potential beneficiary populations and groups (in no particular order)		Key questions and preliminary answers			
		Why?	**Who? Where? Age groups, disease stage*,[11], geographical areas**	**When? (at what level of minimum safety and efficacy data?)**	**Availability? (when?, how much?)**
Therapies *(For all interventions considered for use, it is essential to collect and share data to ensure transparency, accountability, and maintenance of public trust; protect from harm, support autonomy and freedom of choice through informed consent, and ensure confidentiality)*	Health-care workers (and other essential staff including burial and sanitation workers)	Utility: Treating HCWs will help them care for others and increase motivation Reciprocity: in turn for their risking their lives	Based on available data, at the time when benefit is likely to be greatest (e.g. early in disease). NB: some interventions are expected to be efficacious and safe as post-exposure prophylaxis.	Promising results in animal models, preferably NHPs; with informed consent	Depends on the situation. Ideally should have adequate supplies for all sick HCWs, but should drug be withheld because only a few treatment courses are available? (see Annex 5)
	Children	Vulnerable group Children have been affected and are at risk of more severe outcomes	Children should be included in trials where possible. Doses (and response) may be different in children.	Doses should be adjusted for body size and blood volumes.	As for HCWs.
	Pregnant women	Very vulnerable, and have often been excluded from public health measures	Mortality from EVD is likely to be higher in pregnant women.	Preferably data on teratogenicity should be available. But even if not available, and if risk of transmission is high, consider giving with informed consent on possible risk to foetus. More frequent and closer observations necessary.	As for HCWs.
	Population in affected areas	It can be ethical to use certain new interventions in a situation such as this (no licensed or approved treatments, high mortality)	Equity among all affected countries, and among different populations in a country; priority setting according to ethical framework. There should be no discrimination based on characteristics such as gender, race, ethnicity, national origin, education, religion, political affiliation, income or social status. NB: some interventions are expected to be efficacious and safe as post-exposure prophylaxis.	Promising results in animal models, preferably NHPs; based on assessment of risks and benefits; with informed consent.	As for HCWs.
	Population in countries	Untested therapy (do no	Not applicable if not sick	Promising results in animal models,	Priority is to prevent spread

[11] It is very important to obtain more precise information regarding each potential intervention at different time points after infection or disease onset, as preliminary data suggest that some interventions may have limited impact when administered to patients at advanced stages of the disease.

Potential beneficiary populations and groups (in no particular order)		Key questions and preliminary answers			
		Why?	**Who? Where? Age groups, disease stage*,[11], geographical areas**	**When? (at what level of minimum safety and efficacy data?)**	**Availability? (when?, how much?)**
	sharing land borders with areas of active transmission (no evidence of disease or infection)	harm)		preferably NHPs, availability of human safety data; with informed consent.	and infection. Only when there are adequate supplies to provide for possible treatment to these areas.
	Other				
Vaccines	Health-care workers (and other essential staff including burial and sanitation workers)	Utility: Treating HCWs will help them care for others and increase motivation. Reciprocity: in turn for them risking their lives.	If adequate supplies are available, prioritize first HCWs taking care of sick patients in hospitals, then those who may see them in outpatient settings.[12]	Efficacy in NHPs, preferably human safety data, with informed consent.	As soon as available, ensuring that prioritization is done based on a previously agreed upon framework (see Annex 5), vaccine is administered in a transparent fashion and appropriate data are collected.
	Children	Vulnerable group. Children have been affected and are at risk of more severe outcomes.	Children should be offered an opportunity to take part in trials. Doses and immune response may be different in the children.	Are any special additional safeguards needed?	As above.
	Pregnant women	Very vulnerable and have often been excluded from public health measures.	Mortality from EVD is likely to be higher in pregnant women.	Preferably data on teratogenicity should be available. But even if not available, and if risk of transmission is high, consider giving with informed consent on possible risk to foetus. More frequent and closer observations necessary.	As above.
	Population in affected areas	Reduce transmission of disease, save lives	Persons at greatest risk of complications, including death, from EVD. There should be no discrimination based on characteristics such as gender, race, ethnicity, national origin, education, religion, political affiliation, income or social status.	Efficacy in NHPs, documentation of human safety data.	As above.
	Population in countries sharing land borders with areas of active	Protect them from spread into their communities (if supplies are adequate, and	When adequate numbers of doses are available, can prevent spread and stop transmission.	When adequate safety and immunogenicity data are available.	Will depend upon ability to scale-up production – not likely in short run.

[12] NB: will it be necessary to ascertain a priori if they already have been exposed?

Potential beneficiary populations and groups (in no particular order)		Key questions and preliminary answers			
		Why?	**Who? Where? Age groups, disease stage*,[11], geographical areas**	**When? (at what level of minimum safety and efficacy data?)**	**Availability? (when?, how much?)**
	transmission (no evidence of disease or infection)	safety and efficacy are demonstrated).			
	Other				

3.5 Major issues regarding data collection outside of Randomized Control Trials (RTCs)

The use of potential therapies and vaccines outside the context of randomized trials can provide an invaluable opportunity to collect additional efficacy and safety information. This is especially vital considering that for many of the therapies available quantities are very limited.

Communication and exchange of information is critical. Data should be available to inform decisions, but it may be difficult to obtain when there is a need to preserve patient confidentiality and economic interests.

With attention to patient confidentiality it is nevertheless imperative that all data arising from observational studies, compassionate use, or designed trials be shared openly to inform policy-making, patient care, and disease control.

The ability to monitor the effectiveness of these therapies and vaccines and the importance of long term monitoring of individuals who received these interventions is a moral obligation, in order to learn as much as possible about the effectiveness of these interventions as they relate to future use.

As discussed under section 2.2, it is important to have an agreed mechanism that could have real-time access to all the data and would allow all data to be evaluated in real-time to permit adaptation of interventions as more data becomes available.

A minimum set of data should be collected from each dose of the intervention that is used. The ISARIC Ebola Rapid Case Reporting Form (*CRF-Tier 0 Draft 1,* see Annex 6) was designed to facilitate the collection of minimum data together with a *Draft Clinical Characterisation Protocol for Severe Emerging Infections - VHF 01SEP2014 (*see Annex 7). Furthermore, the ISARIC website (www.isaric.org) provides additional CRFs for settings where resources allow for more complex assessments. The data to be collected needs to be feasible under the field realities in affected countries. An online, open-access database which hosts the electronic case report forms for viral haemorrhagic fevers and outbreak protocols is available at www.cliresdms.org.

3.6 Major issues in relation to risk assessment and risk mitigation and management

Managing risk: assessing, mitigating, and communicating the risks around the use of unproven interventions

Given that usual standards of clinical assessment for the proposed interventions have not been met, there is an urgent need to consider the risks of providing such unproven interventions in these circumstances and how best to manage and communicate those risks. Addressing those requires a management approach which includes risk assessment, risk mitigation, and risk communication.

Risk assessment

Efforts to accelerate production and availability of the interventions will make these available, but not for everyone and not in every setting. Several generic risks can be identified that reflect the special circumstances under which these interventions will become available, including the fact that many of them will initially be in limited supply.

- **Perceptions of experimentation**: Conversely, should an intervention have unexpected serious side effects, the perception may be that it was an imposed 'experiment'. Beliefs that there are hidden agendas and interests pushing specific interventions can surface.

- **Clinical trial structure**: In order to elicit evidence of effect, it will be necessary to compare what happens in patients who receive the intervention with the clinical course of similar patients who do not receive it. This will raise questions of fairness and will be difficult to defend, unless it is clear that as soon as there is confidence the intervention is effective and carries limited risk, it will be made as widely available as possible.
- **Equitable distribution:** Interventions found to be effective are unlikely to be available in large quantities, and the need for scientific rigor, appropriate settings and clinical circumstances will mean that there will be only limited access to these interventions at selected sites. Thus issues of fair distribution and prioritization will come to the fore. Demand will be great and the resentment of those denied access intense.
- **Opposition to vaccines and medical treatments** may strengthen, affecting other areas of public health.
- **Reputational risks:** Blame for not providing treatment, and, conversely, perception that experimental treatments have been forced on people to benefit the pharmaceutical industry.

These are generalizations. We have a long list of interventions and each have their own set of questions around efficacy, availability, and adverse effects. These risks have to be mapped out, analysing the likelihood of their occurrence and potential impact.

Risk mitigation

An effective means of mitigating risk is provision of the most recent, accurate, and comprehensible information about the safety and effectiveness of the interventions being considered, while at the same time being proactive and transparent and addressing people's concerns and fears, however founded they are.

All data relevant to implementation of those interventions should be shared as fully and transparently as possible. Information needs to be provided in a form that can be digested by the relevant audiences. Understanding perceptions, beliefs, and values around the subject is crucial to determining how best to provide information and what sort of information and messages are needed. Researching beliefs, perceptions, and values is an essential first step to mitigating risk. The safety profile should be communicated using what we have learned from surveys of beliefs and perceptions. Monitoring of risk should be reasonably straightforward if interventions are implemented through clinical research, as this is an integral component of those protocols. In the case of compassionate use, provisions for documenting unexpected events and the possibility of further investigating those should be recommended. This is likely to prove highly complex.

Communicating issues around access will require explanation of the need to monitor first use and determine its safety before providing it generally. If an intervention proves very effective, messaging should indicate that every effort will be made to provide it more widely. However, such messaging will depend on what the intervention is and how feasible it is to step up production to make it so available.

Risk communication

WHO's own outbreak communications principles[13] outline the need to be the first to make the announcement (i.e. communicate with authority) in an outbreak; be transparent: build trust, conduct communications surveillance about what people know, believe, and fear; and incorporate

[13] Outbreak Communications, WHO 2003

planning throughout outbreak communications. A strategic communications approach needs to be developed and implemented well before the treatments and vaccines are available for public use.

Single Overarching Communication Objective
'People (patients, families, health professionals, decision makers) trust and accept the use of experimental interventions under the conditions proscribed'

Audience mapping*:* Understanding the audience is essential for effectively communicating risk. In this instance, audiences identified include:

- **Primary audiences**: providers and users of treatments and vaccines: Decision-makers, health professionals, emergency responders, and people affected by EVD (patients, families, care givers);
- **Secondary audiences**: those who influence the primary audience (general public, governments, member states, partners, "blockers and opponents"); and
- **Gatekeepers:** groups that can amplify, diminish, distort, or otherwise influence our messages (e.g., media, interest groups, on-line communities, community-based organizations).

Approaches:

Key approaches include recognizing and responding to the following issues:

- 'the public health imperative'- preventable morbidity and mortality;
- fairness, equity and ethics;
- risk perception (the public perceive risk very differently to scientists and experts);
- integration in the overall response to the EVD outbreak;
- use of evidence; and
- building and maintaining trust.

3.7 Major logistics considerations for each investigational therapy and/or vaccine

Given the health infrastructure and personnel challenges in the areas affected by Ebola, decisions on what interventions to use must include logistic considerations. For all these interventions, decisions about implementation will depend upon the appropriateness of the intervention in the specific situation, the availability and quality of data to support the decision on use, the available supply now and in the coming months, and the feasibility of shipping (if required) of the intervention to West Africa. Countries face multiple logistical constraints, including the ability to safely and securely transport the intervention to the delivery site, the existence of safe and secure storage facilities with appropriate cold chain capacity, the availability of sterile equipment to administer injections and/or infusions, clean water for oral medications, trained and experienced health-care providers to administer the interventions, and the ability to recognize and manage adverse events associated with treatment, such as allergies.[14]

[14] Given the fact that this outbreak has international public health implications, it is expected that countries as part of a coordinated effort, with the support of the international community, will work to address each of the logistics challenges in the short term and will develop plans for sustainable strategies to address the logistics challenges in the long term.

Table 6. Summary of potential therapies and vaccines according to selected logistics considerations

Type of intervention	Administration route	Storage	Remarks
Therapeutic			
Immunoglobulins			
Convalescent plasma	IM, IV equipment and supplies for sterile injection and/or infusion; HCWs can administer	Commercial IVIGs may be stored at room temperature; however these contain stabilizers and are pH-controlled. May require refrigeration and rewarming before transfusion.	Identifying PCR-negative donors; local capabilities for Ebola testing; ensuring donations are negative for HBV, HIV, HCV, and other blood-borne pathogens; availability of plasmapheresis infrastructure; consider using units from 2 or more donors because of variation in immune responses. Small risk of anaphylactic reactions with IM or IV administration; need ability to administer epinephrine and antihistamines +/- corticosteroids if this is observed; aseptic meningitis has been reported following IVIG (Kato); IV infusion of IVIG may take 2-5 hrs, with frequent monitoring of vital signs (complications more frequent with rapid infusions, particularly in patients with acute infections; premedication with acetaminophen, diphenhydramine, corticosteroids (hydrocortisone 6 mg/kg for children; 100-150 mg for adults) 30' in advance of infusion may prevent severe reactions). IVIG inhibits response to measles and other vaccines.
ZMapp	IV equipment and supplies for sterile infusion; HCWs can administer	Shipping and storage at -20°C. MappBio currently gathering stability data to determine stability at 4°C. Antibody preparations should be stored in small aliquots and thawed once; repeated freezing and thawing may negatively impact antibody – hence frost-free freezers are not appropriate, as they alternate between freezing and thawing.	Shipping from source of production to point of use, local transport, and storage. Limited to no current supply. Appropriate freezers to ensure avoiding repeated freeze-thaw cycles.
Hyperimmune	IM or IV depending on	Other hyperimmune globulins	Not yet available.

Type of intervention	Administration route	Storage	Remarks
globulin from animal plasma	volume needed (?) - equipment and supplies for sterile injection and/or infusion; HCWs can administer	(e.g., TIG and RIG) should be stored at 2-8°C and should not be frozen.	
Antiviral small inhibitory RNA			
TKM-100802 (Lipid nanoparticle siRNAs)	IV equipment and supplies for sterile infusion; HCWs can administer	Lyophilized LNP stable at 40°C	FDA-authorized emergency use in infected patients for therapeutic or post-exposure use; dose-related transient tolerable side effects related to cytokine release if at high dose. Requires IV infusion equipment and staff
AVI 7537 (phosphorodiamidate siRNA) antisense RNA	IV equipment and supplies for sterile infusion; HCWs can administer	Product is stored in bulk at 2-8°C, for stability, but after fill/finish and lyophylized, stable at room temp for months; vials have been retested for stability at 12-18 months with good results.	Requires IV infusion equipment and staff
Immunomodulators			
Interferons (Type 1 [α,β])	SQ/IM equipment and supplies for sterile infusion; HCWs can administer	Store at 2-8°C. Do not leave out of refrigerator for >24h. Do not freeze or shake. Protect from light (instructions for PEGASYS peginterferon α-2a for subcutaneous use).	In Ebola rhesus macaque model, administration of interferon x 9 d prolonged time to death; did not increase survival. Flu-like symptoms (fever, myalgia, chills, etc.) not uncommon with interferon injections – can potentially confound diagnosis / prognosis; anaphylaxis can occur. Contraindicated in combination with ribavirin in women who may become pregnant – teratogenic.
Antiviral drugs			
Favipiravir/T-705	Oral	Stable at room temperature	Up to 18 tablets per day to be swallowed (depending on

Type of intervention	Administration route	Storage	Remarks
			dose) – may present challenge for compliance in patients with nausea. Contraception should be used during and up to 7 days after treatment. Need to exclude pregnant women for whom the drug is contraindicated – may need pregnancy testing
BCX4430	IM equipment and supplies for sterile injection; HCWs can administer	Probably stable at room temperature	NHP studies in progress. No human safety data available yet. Phase 1 studies planned late 2014.

Type of intervention	Administration route	Storage	Remarks
Vaccines			
ChimpAdeno3	IM equipment and supplies for sterile injection; HCWs can administer	Storage at -70°C	Tested in 16 NHP with 100% protection. Approximately 200 doses (bivalent) available for Phase I trial to begin in US in September 2014; preliminary safety data may be available October 2014. Likely to require special freezing facilities (e.g. liquid nitrogen) that could make transport complex.
rVSV	IM equipment and supplies for sterile injection; HCWs can administer	Storage probably at -70°C	Tested in 20 NHP with 100% protection. Theoretical risk of replication raises safety concerns. No human safety data. Safety in immunocompromised patients is unknown. Phase I trial planned in US. Likely to require special freezing facilities (e.g. liquid nitrogen) that could make transport complex).

3.8 Preliminary considerations regarding management of future supplies

As more treatment courses and vaccines doses may become available in the future, it is important to include in the deliberations some mechanisms that could assist with their distribution to countries. At an international level, options include:

- *ICG-Like:* A partnership with technical experience in emergency response, 24/7 availability, with institutional logistic and implementation rather than solely scientific expertise. There is experience with this mechanism in the management of the Yellow Fever vaccine stockpile.

    - Pros: Decisions are made by consensus, quickly in 48h, and shipments within 3 days
    - Cons: Different organizational interests may make consensus difficult. The appropriate expertise and national interests may not be adequately represented in the group.

- *International Health Regulations Emergency Committee*: The WHO Director General can convene an Emergency Committee under the International Health Regulations to advise the WHO Director General if the event should be considered a Public Health Emergency of International Concern (PHEIC), and to advise temporary measures, which might include dispensing contents of stockpile or other sources of the MCMs.

    - Pros: The WHO Director General can establish a group of appropriately qualified experts
    - Cons: There is a risk of delays in nominations, availability of experts, making decisions. Demands for geographic representation may conflict with the demands for appropriate expertise and contextual knowledge.

- *Standing Committee*. A Standing Committee is formed of appropriate experts, including public health experts from WHO regions, and relevant partners. When an event, which might require administration of therapies and/or vaccines, is recognized and a request is received, the Committee meets, incorporating relevant representation from the affected Member States. The Committee decides on the distribution of the therapies and/or in the context of essential information about the event as provided by the affected Member States.

In addition, within each country, transparent and participatory processes should be established to define the criteria for prioritization to various groups. The aim is to engage the affected communities and to reach mutual agreement and buy-in to the extent possible.

4. COMMUNICATION CONSIDERATIONS

Communication efforts need to address concerns about inequity in the risk of the disease, the social costs of the disease and its management, and tendencies to attribute blame and seek retribution. The development of messages and communication strategies should benefit from inputs from the community (e.g., by involving civil society representatives as appropriate).

The goals of communication efforts should be to:

- Foster respect and trust among all parties affected by and supporting the effort to stop transmission of the disease;
- Empower affected communities to respond to the epidemic;
- Enhance understanding and allay local fears and anxieties about the disease;
- Build credibility of scientific and health-care efforts; and
- Influence attitude and behaviour change.

4.1 Objectives

This section is intended as a resource to support communication by Ministries of Health in African countries on potential experimental treatments and vaccines for Ebola.

With regards to communications activities, opportunities exist to:

1. **Disseminate timely and accurate messaging about potential future** interventions for the treatment or prevention of Ebola (and interventions that are not effective), targeting local public health experts, health-care workers, and communities.
2. **Reinforce life-saving and outbreak control public communications** on how to prevent the spread of the virus while promoting care-seeking behaviours for those already affected.

4.2 Principles of communication

Box 4. Summary of principles to guide communications planning in emergency settings

In an emergency, maintain the following principles when planning communications[15]:

- **Coordinate**. Identify communication partners and coordination mechanisms to support the exchange of materials and messaging or joint decision-making.
- **Announce early** to prevent misinformation and rumours, even with incomplete information.
- **Be transparent**. Communicate facts as and when they are available.
- **Create mechanisms for dialogue** that allow the population to express their concerns.
- **Use targeted messaging** to specific groups, the general population, or health-care personnel.
- **Practise positive communication** to avoid panic. Reiterate simple preventive measures and describe appropriate behaviours that can be successfully adopted by the population.
- **Listen.** Proactively prevent and address rumours. Put mechanisms in place to detect the early diffusion of rumours. Have responses prepared in advance.

[15] Adapted from "*World Health Organization Outbreak Communication Planning Guide"* (PDF). Geneva: World Health Organization, 2008. Available at http://www.who.int/ihr/elibrary/WHOOutbreakCommsPlanngGuide.pdf.

4.3 Communications planning

Shortly after the Geneva consultation, WHO Headquarters released a statement to global media containing high-level outcomes and related messaging.[16]

To accompany this information, Health Ministry policymakers are encouraged to prepare a proactive communication plan that considers the above objectives and principles.

The following activities are suggested, targeting two distinct audiences:

- **Primary:** Briefing media, academics, community leaders, and local and international health organizations on potential future interventions for treatment and prevention.
- **Secondary:** Disseminating a fact sheet on "*Potential Therapies and Vaccines in the Pipeline*" to health workers in facilities and in communities conducting door-to-door activities. The fact sheet can be based on the summary information and questions and answers below.

4.4 Summary of options for potential therapies and vaccines

To support in-country communications by Ministries of Health in Africa, the following table provides a summary of potential therapies and two main vaccines for the EVD, as well as what is known about safety and availability.

Table 6. Summary for communications strategy

Status	Safety / Efficacy	Availability
Therapies (up to 10 potential options)		
The potential products under consideration are at an experimental or early stage of development and investigation.	For most therapies, there is limited data on their safety and efficacy in humans against Ebola. There are plans for accelerated studies and the results from these studies are expected late this year or in early 2015.	Despite a growing number of new interventions, quantities will be very limited. Supplies of all interventions will not meet demand in coming months.
Vaccines (two potential options)		
There are two leading vaccines, both currently unlicensed. Phase I trials have begun in Africa, the EU, and the US. At the same time both are being considered for use in targeted groups in Africa.	For both vaccines, there is limited data or no data on their safety and efficacy in humans against Ebola. Phase I trials are underway and the results from these studies are expected late this year or in early 2015.	Both vaccine candidates are being fast-tracked and several thousand doses may be available in late 2014 for clinical testing of efficacy / effectiveness and for compassionate use.

[16] Consultation on potential Ebola therapies and vaccines. Geneva: World Health Organization, September 2014. Available at: http://www.who.int/mediacentre/events/meetings/2014/ebola-interventions/en/.

Box 5. Questions and Answers

Below are examples of common questions and suggested responses that may be used in communications about the possible treatments and vaccines available.

1. What treatments and vaccines will be potentially available?

There are a range of possible interventions for treatment and prophylaxis and two (or three) vaccine candidates. None are clinically proven. All interventions have limited information on their safety and efficacy, supplies are very limited, and many require countries and their partners to address practical challenges for administration, for example, cold chain requirements, infrastructure needs, and health worker training.

2. Is there confidence that these interventions will be effective?

As experimental therapies, these medications have not yet been through the full range of clinical testing, therefore we do not yet have full confidence of their safety and efficacy. However, at this stage of the outbreak, it is considered that the possible benefits outweigh the risks for the individuals and communities concerned.

3. When will the interventions be available?

The international community is mobilized and coordinating to fast track the development and clinical evaluation of promising options, which under normal circumstances, may take up to 10 years. This is important because it will provide additional tools for the response to the current outbreak and in preparation for the future. While extraordinary measures are now in place to accelerate the pace of clinical trials, new treatments or vaccines are not expected for widespread use before the end of 2014. Until then, only small quantities of up to few several doses/treatments will be available, and the scale up of production may take longer. It should be noted that the potential compassionate use and further investigation of these compounds should not detract attention from the implementation of effective, supportive clinical care, rigorous standards of practice in infection prevention and control (IPC), careful contact tracing and follow-up, effective risk communication, and social mobilization, which will be crucial to terminate the epidemic.

4. Who will be prioritized to receive the treatments and vaccines that become available?

Given the very limited quantities available, countries will have to establish clear criteria on how the first treatment or vaccine doses will be allocated.

5. How will outcomes be measured?

In order to understand the safety and efficacy of the interventions used, all efforts will be made to collect and share data, including from treatments provided for compassionate use (i.e. use of a drug outside of a clinical trial). Scientific evaluation of the interventions will be used to inform assessments and future decisions. All interventions given will be continuously monitored for possible adverse effects.

6. Is the use of unproven therapies and vaccines unethical?

West Africa is experiencing the largest, most severe, and most complex outbreak of Ebola in history. In these circumstances, it is considered ethical to offer unproven interventions with as yet unknown efficacy and adverse effects in humans. Full transparency about all aspects of care, informed consent, freedom of choice, confidentiality, and preservation of dignity will guide the provision of such interventions.

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