World Health Organization

INTERIM GUIDANCE

Potential Ebola therapies and vaccines

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Contents

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

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 the consultation.

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 1.1 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.

[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
TKM-100802 Lipid nanoparticle small interfering Ribonucleic acid (siRNA) (Tekmira)	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 administered 48 hours after infection and 67% survival 72 hours after infection.	A single-dose study in healthy volunteers found side effects include headache, dizziness, chest tightness, and increased heart rate at high doses. At lower doses, projected to be the dose used for treatment, the drug was better tolerated.	The US Food and Drug Administration (FDA) has authorized emergency use in EVD-infected patients and several such patients have 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 1.2. 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	The rVSV vaccine aims to induce EVD-specific immune	It is unknown if rVSV-EVD will grow in humans, especially in	Safety, efficacy, and duration of protection are unknown. A