WHO convened an expert consultation to consider the use of investigational therapeutics or investigational vaccine(s) for post-exposure prophylaxis (PEP) for frontline healthcare workers (HCWs) potentially exposed to Ebola virus (Zaire ebolavirus) during the current outbreak involving Eastern Democratic Republic of Congo (DRC), 11 September 2018.

Experts:
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Background
WHO convened an expert consultation to consider the use of investigational therapeutics or investigational vaccine(s) for post-exposure prophylaxis (PEP) for frontline healthcare workers (HCWs) potentially exposed to Ebola virus (Zaire ebolavirus) during the current outbreak involving Eastern Democratic Republic of Congo (DRC).

This consultation builds on the foundation of previously published work on post-exposure prophylaxis and the risk of transmission of Ebola virus infection. This consultation addresses current thinking on the issue of PEP for HCWs potentially exposed to Ebola Zaire and considers the more recently available information on some therapies. In addition, the consultants noted some of the practical considerations for the use investigational therapeutics and vaccine as PEP, and also considered the uncertainties and limitations of the available information on the use of PEP.

While this consultation focuses on PEP, the use of proper infection control and prevention methods are essential, including the following:
- A whole safe system of work including use of personal protective equipment (PPE) and proper training and techniques for donning and doffing PPE
- Use of laboratory diagnostics to identify persons with Ebola infection and appropriate levels of infection control measures and patient care

• Considering the use of targeted pre-exposure investigational vaccine for HCWs – ideally vaccination would be administered prior to any potential exposure event consistent with WHO interim recommendations for vaccination of (i) local and international health-care and front-line workers in the affected areas and (ii) health-care and front-line workers in areas at risk of expansion of the outbreak. The consultants recognized that despite the above measures, that circumstances arise where HCWs caring for persons with Ebola infection may be exposed and use of PEP warrants consideration.

Transmission of Ebola virus in HCWs
Transmission of Ebola virus can occur when Ebola virus containing body fluids provide an opportunity for the virus to gain entry into the body of another, such as

- Ebola virus containing body fluids on non-intact skin or mucous membranes
- A percutaneous exposure from a needle that was in contact with the blood from a patient with Ebola

Consultants considered differing levels of risk for different types of exposure events and recommended considerations for possible use of investigational therapies or an investigational vaccine depending on the nature of the exposure event.

Investigational Therapies Considered
The four main investigational therapeutics considered were ZMapp, Remdesivir (GS-5734), REGN3470-3471-3479, and mAb114. A brief description of some of the available data for each is summarized in the WHO statement on Monitored Emergency Use of Unregistered Investigational Interventions (MEURI) for Ebola virus disease (EVD). In addition, despite the considerable uncertainty regarding whether favipiravir provides clinical benefit in patients with Ebola infection, its use for PEP might be considered in select circumstances. (See Data Collection and Clinical Trials.)

The investigational vaccine considered was Merck’s rVSV ZEBOV-GP vaccine (V920). A dose of $5 \times 10^7$ pfu was considered as the vaccine dose for PEP.

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Categorizations of Level of Risk

A categorization of level of risk for a potential Ebola virus exposure event was based on the publication from Fischer WA, et. al.\(^1\)

Table. Categories of Risk of Transmission of Ebola Virus Following Potential Exposure

<table>
<thead>
<tr>
<th>Event</th>
<th>Example Scenarios</th>
<th>Risk of Ebola Virus Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>No direct contact with a patient with Ebola virus disease or their body fluids</td>
<td>Breach of personal protective equipment without risk of contamination</td>
<td>Low</td>
</tr>
<tr>
<td>Intact-skin-only contact with a patient with Ebola virus disease (alive or deceased) or their bodily fluids</td>
<td>Clinical assessment of an individual with suspected Ebola virus disease before diagnosis without appropriate personal protective equipment</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Broken skin or mucous membrane contact with a patient with Ebola virus disease (alive or deceased) or their bodily fluids, penetrating sharps injury from used device or through contaminated gloves or clothing</td>
<td>Bodily fluid in direct contact with eyes, nose, or mouth; penetrating sharps injury from a used intravenous cannula</td>
<td>High</td>
</tr>
</tbody>
</table>


Considerations for PEP Based on Category of Risk

Consultants offered the following recommendations for PEP in HCWs that have been potentially been exposed by level of risk. (See Table.)

High Risk Exposure Events
- For persons that have experienced a high-risk exposure event, the prompt administration (at the earliest possible time within 48-72 hours after the exposure) of one of the four injectable products (ZMapp, Remdesivir, REGN3470-3471-3479, or mAb114) should be strongly considered.

Intermediate Risk Exposure Events
- For persons that have experienced an intermediate risk exposure, the prompt use (at the earliest possible time within 48-72 hours after the exposure) of investigational vaccine should be considered. Given the particular circumstances of the intermediate risk event, there may be reasons to consider the use of a therapeutic agent as PEP, e.g. uncertainty around the risk of transmission. (See Other Factors to Consider – Drug/Vaccine and Vaccine/Drug interactions.)
Low Risk Exposure Events

- For persons that have experienced a low risk exposure event, the administration of an investigational vaccine should be considered, to occur promptly after the exposure event (at the earliest possible time and within 48-72 hours of the exposure event). The use of a therapeutic agent as PEP is not considered in light of the risk benefit ratio. Vaccine-induced immunity is likely not to be rapid enough to consistently prevent Ebola virus disease when administered as PEP, but might potentially still play a role in attenuating clinical disease, should disease occur, and would induce protection from subsequent exposures.

There is considerable uncertainty as to the utility of favipiravir for treatment of Ebola infection and it has relatively weak anti-Ebola virus activity. The fact that favipiravir is available in oral form and supplies may be available may lead some to consider its use as PEP in low and intermediate risk scenarios. Given the uncertainty regarding its utility, if its use is considered, it is recommended that this use be in a randomized controlled trial to assess the risks and benefits.

Data Collection and Clinical Trials

Data should be gathered from consenting patients in any circumstance when an investigational therapeutic is used as PEP, whenever possible to build up the evidence base. If investigational therapeutics for PEP are expected to be used in more than a few instances, implementation of a randomized controlled trial should be strongly considered in order to evaluate the impact of particular investigational therapeutics on Ebola virus infection when administered post-exposure.

Other Factors to Consider

- Drug/Vaccine or Vaccine/Drug or Drug/Drug interactions
  - If vaccine and an antibody-based therapeutic are administered concurrently it is likely that the antibody-based therapeutic may bind the vaccine antigen and reduce the vaccine-induced immune response. It is also possible that some amount of antibody may bind vaccine antigen potentially reducing the amount of antibody therapeutic available to treat an Ebola infection in a patient with EVD.
  - It is expected that vaccine should provide good protection, 10 days or more after vaccination.
  - Based on published data, remdesivir does not appear to interfere with the replication of VSV, suggesting that remdesivir is not likely to interfere with the concurrent administration of the Merck v902 investigational vaccine. Remdesivir did not inhibit VSV replication in cell culture assays in Hela cells at a remdesivir concentration of 10uM. Favipiravir has antiviral activity in cell culture assays against a number of different viruses. Favipiravir’s effect on VSV replication has not been published, however, in a preliminary study.

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study Favipiravir inhibited VSV replication in Hela cells with an EC50 of ~150uM. Further, Rabies virus (a virus from the same family as VSV) replication is inhibited by favipiravir. These data may suggest a likelihood that favipiravir could interfere with the concurrent administration of the Merck v902 investigational vaccine (a VSV-based vaccine).

- For exposures occurring among a vaccinated person, e.g.
  - if the vaccination occurred ≥ 10 days before the exposure event, any of the four injectable products could be considered;
  - if the vaccination occurred < 10 days before the exposure event, there are a number of different factors that would need to be weighed to decide how to proceed with an individual patient.

- There is no evidence on the use of combinations of investigational therapies as PEP to inform the benefits and risks of uses of combinations including questions of non-interference and safety concerns. Such evidence on treatment use of combinations for human EVD is also scarce.

- Drug Supply Considerations and Number of Persons Exposed
  - It is reasonable to consider the number of persons exposed and the available drug supply, as the supply for some products is limited. Priority should be given to the (1) use in a clinical trial and (2) treatment of patients with confirmed Ebola virus disease in case of limited supply.

- Timing of Vaccine, Post-vaccination Fever, and Monitoring for Ebola Infection
  - Depending on the timing of when vaccine is administered relative to the time of the Ebola exposure, it is possible that a post-vaccination fever could occur during the same time period when one fever from Ebola infection could occur. Should this circumstance arise, it is important to consider how the etiology for the observed fever will be assessed (post-vaccination fever vs. fever from Ebola infection vs. other source for fever). We note that it may be helpful to consider the ring vaccination standard operating procedure as an approach that could be utilized for such circumstances. In addition, PCR-based testing for the Ebola virus glycoprotein region may be positive in the setting of the nucleic acid from the VSV based vaccine, making it difficult to rely on PCR based testing after VSV (V902) vaccine as the means for differentiating Ebola infection from post-vaccination fever. It is also important to consider appropriate isolation procedures for persons being assessed for post-vaccination fever vs. Ebola infection vs. other causes of fever.

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Assessment of conflicts of interest

WHO requested all experts to complete the WHO DOI form and return the completed form to WHO before the meeting. Completed DOI forms were received from all participants. The following interests were declared:

1. Dr Armand Sprecher was an advisor that provided an independent analysis during a legal proceeding in an UK court, as someone with experience in the management of EVD. This was not deemed a significant conflict of interest.

2. Dr Michael Jacobs has been invited to a meeting organized by Gilead to enable him to share the UK experience of using experimental therapies (of all types) for high consequence infections and discuss future access and trials. The cost of his return flight is covered by Gilead. This is not a paid advisory meeting and Dr Jacobs will not receive any remuneration personally. This was not deemed a significant conflict of interest.
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