Sudan Ebolavirus Candidate Vaccines

What additional research should be conducted to advance the evaluation of these candidate vaccines?

SUMMARY OF THE DELIBERATIONS

12 January 2023
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Background and meeting goals

Sudan ebolavirus (SUDV) maintains itself in wild animals and humans are initially infected via animal exposure. SUDV causes severe disease, though compared to Ebola Zaire (ZEBOV) (~50% case fatality [CFR] in the past), SUDV has a slightly lower CFR with reduced incidence of other symptoms. SUDV infection is most common in ages 20-39 years.

The recent outbreak of SUDV in Uganda, which started on 20 September 2022, was declared over on 11 January 2023 after 142 reported cases with 55 deaths\(^1\). The outbreak was driven by two major clusters. Control was achieved primarily by Ugandan leadership & teamwork to achieve risk communication, community engagement, epidemiologic methods & surveillance (including contact tracing) with case management, and prevention & control.

Within 79 days of the declaration of the outbreak, a clinical trial was designed and approved, a trial team was ready to start, and vaccines were placed in vials for study. Other public health measures ended the outbreak before the trial could begin.

This experience raises the question of how the world can be better prepared for a subsequent SUDV (or other) filovirus or emerging pathogen outbreak.

Recognizing that it is an essential part of WHO’s constitution and mission to integrate research into emergency response, the meeting focused on preparing for the next outbreak, fully using assets & human resources now in place as part of the previous outbreak response.

The key questions addressed during the expert consultation included:
- how to advance evaluation of vaccines to support future prioritization and possible future regulatory authorizations, and
- what data could help with policy decisions

This report summarizes the deliberations and key emerging messages. It does not purport to be a verbatim record of the meeting.

Copies of all presentations and the recording of the meeting can be consulted at this link: https://www.who.int/news-room/events/detail/2023/01/12/default-calendar/save-the-date---sudan-ebolavirus-candidate-vaccines---what-additional-research-should-be-conducted-to-advance-the-evaluation-of-these-vaccines

Additional information on research & development matters can be accessed at this link: https://www.who.int/teams/blueprint/ebolavirus

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\(^1\) https://www.afro.who.int/countries/publications?country=879
Progress on candidate vaccines development and evaluation

Investigators in Uganda rapidly prepared to perform an RCTs and an add-on study in record time. The Tokomeza ring vaccination trial of 3 candidates, comparing results after immediate vs 21 days delayed vaccination was designed to study vaccine efficacy in 6-year-old and older contacts of SUDV cases with 21 days safety follow-up. An add-on study, the Tokomeza Plus study was designed to provide complementary information on immune response (cellular & humoral) post vaccination among the ring vaccination volunteers.

The Tokomeza trial was approved within 9 weeks of protocol submission and the candidate vaccines doses started to arrive in Uganda only 79 days after the outbreak declaration, roughly coinciding with the outbreak end. Teamwork and a South-to-South collaboration, political support, and use of technology (including electronic data collection systems) were keys to the prompt preparatory actions.

Table 1. Vaccines considered for inclusion in the Tokomeza ring vaccination trial in Uganda, 2022

<table>
<thead>
<tr>
<th>Type of vaccine</th>
<th>Vaccine developer</th>
<th>Viruses targeted</th>
<th>No. of doses</th>
<th>Immunogenicity + safety in humans?</th>
<th>Efficacy against SUDV in animals?</th>
</tr>
</thead>
<tbody>
<tr>
<td>cAd3</td>
<td>Sabin Vaccine Institute + US NIH</td>
<td>Sudan ebolavirus</td>
<td>Single</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>cAdOx1</td>
<td>University of Oxford</td>
<td>Sudan + Zaire ebolaviruses</td>
<td>Single</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>rVSV SUDV</td>
<td>Merck/IAVI</td>
<td>Sudan ebolavirus</td>
<td>Single</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

The vaccines prepared for use in the recently ended outbreak, all of which are configured as single-dose vaccines, included:

**ChAd3 (Chimpanzee adenovirus 3)-vectored candidate vaccine**

It is based on the previously tested GSK ZEBOV vaccine. To date, studies have been performed in NHPs with challenge using Boniface and Gulu strains of SUDV, which were reported to show protection up to 12 months and to yield a potential candidate correlate of protection. US & Uganda Phase 1 trials are complete and phase 2 trial is planned in Africa. Planned regulatory pathway: animal rule but open to other pathways.

**ChAdOx1 (Chimpanzee adenovirus Oxford, strain 1)-vectored candidate vaccine**

It is based on same platform used for the COVID vaccine. Phase 1 trials complete and additional phase 1 studies ongoing. The immune response lasts at least 6 months. The vaccine will be manufactured by Serum Institute of India.

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4 https://www.ox.ac.uk/news/2021-11-11-ebola-vaccine-begin-human-trials
VSV-vectored candidate vaccine

NHP efficacy studies are complete. No safety data in humans is yet available. The developer plans dose ranging and a manufacturer comparison study with Phase 1 in US, Phase 1/2 in Uganda in HCW, with exploration of immunobridging from Ervebo to Sudan candidate as a potential approach to authorization.

Preparing for the inevitable and faster

In Uganda in 2022, under the leadership of the Ugandan MoH, and with WHO and partners, a workable trial of ring vaccination of SUDV disease case-contacts was planned and established in record 9 weeks after the outbreak declaration, but the outbreak ended just as it became ready to start. In a future outbreak, can trials start within 14 days of the outbreak being declared?

Several opportunities were identified during the Uganda outbreak for accelerating the response in a subsequent outbreak. Preparation (vialing and testing) of doses took the longest but the experience has helped those involved to identify other opportunities to fast-tracking the initiation of research integrated early on into the outbreak response including:

- earlier access and additional data for candidate vaccines prioritization,
- design and pre-approval of simple trial protocols and faster regulatory and ethical approval process,
- anticipatory preparation of teams for trial and logistics,
- having vailed candidate vaccines available and ready for international export/import,
- addressing legal framework and liability and insurance issues (to make sure that all investigators are covered, not just developers), and
- identifying flexible sources of funding to support rapid initiation of trial activities as part of outbreak response.

Figure 1. A global collaborative effort accelerated many key actions during the preparations of the Tokomeza trial, 2022

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5 https://www.iavi.org/our-science/emerging-infectious-diseases-vaccines-and-therapeutics
Goals of research during an inter-outbreak period

The goal of additional SUDV vaccine research during an inter-outbreak period is to advance evaluation of candidate vaccines in order to support future prioritization and possible future regulatory pathways towards an authorized or licensed product (potentially including under EMA article 58 now called M4All).

Future prioritization of candidate vaccines

The size and rapid end of the recent outbreak indicates that it may be challenging to plan for simultaneous testing of several vaccines in such a trial, and thus, data that will assist in prioritization of vaccine candidates for entry into a trial will be important to collect in the interim. In The WHO vaccines prioritization Working Group provided recommendations on candidate vaccines to include as soon as data was available for their review.6

In addition, decisions on which candidate vaccines to maintain into vials (as a reserve of investigational doses in preparation for future outbreaks) will need to be informed by data.

Data that could support rapid regulatory authorization/licensure

Additional information from human and animal studies might support licensure or authorization before a clinical efficacy data is available.

Therefore, studies should aim to collect reliable safety (preferably with placebo control in the at-risk populations) and immunogenicity studies of the candidate vaccine(s) completed well beforehand, when there is no outbreak.

Simpler study designs during outbreaks

A ring vaccination study in a subsequent outbreak, including randomized studies (e.g. Ebola ça suffit7) or without randomization (e.g. Guinea8 and DRC expanded Access/Compassionate Use9,10), or deployment of a vaccine authorized using alternative regulatory pathways can be greatly simplified by not having to monitor immunogenicity or safety (except for SAEs involving hospitalisation or death).

Reliable previous safety studies would also simplify the informed consent process. Such studies will also provide robust data to support vaccine efficacy claims based on alternative regulatory pathways.

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7 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)61117-5/fulltext
8 https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(17)30541-8/fulltext
How to advance candidate vaccines evaluation during the inter-outbreak period?

Priority animal studies
Animal studies can support vaccine development, but need to be carefully designed, and assay need to be standardized, especially where animal results are bridged to humans (as in the “animal rule”) or where comparisons are made across experiments.

Non-Human Primates (NHPs) are considered the most useful animal model for predicting SUDV outcomes in humans. There are concerns that there are differences among NHP species to filovirus susceptibility and that results in animals may also differ by virus strain.

Nonetheless, studies using passive transfer to evaluate the protective responses against ZEBOV vs. SUDV could help to establish the relative importance of cell-mediated vs. humoral immunity for these viruses, addressing a key concern in immunobridging across viral species.

Inter-outbreak clinical studies
Giving the paucity of data available, none of the existing vaccines are currently suitable for use outside of a clinical trial.

- Clinical trials should generate data that will move these investigational products closer to regulatory authorization or licensure.
- Clinical trial phases can be seamless especially in an epidemic, but traditional phase 1 and phase 2 activities can and should be conducted during the inter-outbreak period.
- Clinical trial monitoring to assure data quality is important to assure that trials will yield useful data.
- Clinical endpoints that can be studied in the inter-outbreak period that are on the critical path to vaccine regulatory authorization/licensure include immunogenicity data and safety data.
- Collection and handling of samples is simplified if there is no risk of SUDV contamination. These data can also inform decisions on candidate vaccine(s) prioritization.
- Other factors will also influence prioritization decision such as the results of NHP studies, including extent of safety data, likely availability of needed numbers of doses, previous data with the vaccine platform, manufacturing considerations, deployability, etc.
Why should we promote the availability of additional clinical immunogenicity data?

Immunogenicity data can provide an improved basis for prioritization among vaccines, especially where samples are taken from recipients of multiple vaccines in the same trial, evaluated in the same validated and standardized assays. At the very least candidate vaccines should be evaluated using the same validated and standardized assays. While immune parameters that predict protection are not known and may vary from one vaccine to the other, evaluation of immunological parameters (including cell-mediated responses) will be an important input to decision-making.

Long term immunogenicity data may inform need for boosting, although correlation of immune markers to protection in the longer term can be different than in the short term. Also consider quality aspects for immunobridging. Durability of immune response could help in planning possible boosting, recognizing that the likely primary use of a vaccine will be in ring vaccination where durability of response may not be critical.

Can immunobridging accelerate the regulatory evaluation process?

The Janssen ZEBOV vaccine was licensed via immunobridging from NHP to humans.\(^\text{11}\) Binding antibody, neutralizing antibody, and T cell responses were all induced but humoral responses were more predictive of protection than cellular responses, though T cell responses also contained independent information.

For example, the US FDA animal rule\(^\text{12}\) is also a potential mechanism for approval if approval via other approaches is not possible because of the lack of endemic disease or because of the lethal nature of the disease, it would not be ethical or feasible to conduct human efficacy studies.

The potential to use immunobridging approaches, supported by animal data, to support efficacy of a vaccine using the same platform as a licensed ZEBOV vaccine has been considered. While SUDV and ZEBOV are different species of virus, there are similarities in their virology and pathogenesis.

While all experts expressed a strong preference for clinical efficacy data, some expressed openness to this type of immunobridging approach and others raised concern that uncertainties regarding the relative contribution of different immune mechanisms to protection from each virus reduce confidence in using cross-virus immunobridging to establish efficacy. Additional data on this topic, as well as immune profiling of each virus including protective cellular immune responses could reduce uncertainty regarding cross-virus immunobridging.

The experts did not discuss whether there was more vs. less comfort with immunobridging across target species (e.g., from NHPs to humans, as was done for the Janssen EBOV vaccine or would be done for an animal rule approval) vs. across related viruses (from ZEBOV to SUDV) in the same target species (humans). Nonetheless, this is an important issue to consider.

\(^{12}\) https://www.fda.gov/drugs/nda-and-bla-approvals/animal-rule-approvals
**Should safety data be collected in advance?**

These data are also on the critical path to vaccine development. More safety data will support conduct of later-phase clinical trials and the entire safety database needed to support licensure (typically around 3000 vaccine recipients) could be collected in the inter-outbreak period.

Both safety and immunogenicity should be also studied in people representative of those who will receive vaccines during and in preparation for a future outbreak.

**Why assay development, standardization and validation is important?**

Currently existing assays include a qualified IgG ELISA (similar to FANG ELISA) and a rVSV pseudo-neutralization assay (which may not be useful for rVSV vaccines). T cell assays exist also. Standardization of assays across vaccines should be done if possible. CEPI is funding a human standard antibody preparation. Standardization and validation of methods/assays is important, which will enable performing a core set of immune response assays for all vaccines.

**What other studies can be considered (not in the critical path)?**

Studies of other clinical outcomes could provide useful information but were not considered as high a priority in the discussions. This includes study of vaccine immunogenicity in survivors or their contacts and study of heterologous regimens (which require better understanding of potential role of vaccines in the immune response and likely could only be evaluated in collaborative studies).

Observational studies as those describe above would be useful for post authorization confirmation.

**Table 2. Candidate vaccines: doses ready to use for trial or deployment**

*Data as of January 12, 2023*  

<table>
<thead>
<tr>
<th>Doses in 2023</th>
<th>chAd3</th>
<th>chAdOx1</th>
<th>VSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Uganda</td>
<td>1,096</td>
<td>2,000</td>
<td>2,200</td>
</tr>
<tr>
<td>With developer/manufacturer</td>
<td>Nearly 10,000</td>
<td>40,000</td>
<td>Nearly 95,000</td>
</tr>
<tr>
<td>Additional doses</td>
<td>Several thousands</td>
<td>Several hundred thousands</td>
<td>Several thousands</td>
</tr>
</tbody>
</table>

*Preliminary estimates subject to changes*
Studies during outbreaks

During outbreaks the aim is the rapid start of studies integrated into initial outbreak response or the prompt deployment if a candidate vaccine has been prioritized and documented to be efficacious.

Super simple protocols

Collection of sufficient safety and immunogenicity data prior to an outbreak could allow clinical trials during outbreaks to focus their resources on collecting efficacy data with fewer complexities. Trials can be initiated quickly during an outbreak if they are simple enough.

Key needs to initiate a trial include:

- Available doses in vials of pre-prioritized vaccines.
- Reliable safety and immunogenicity studies of the prioritised vaccine(s) completed well beforehand when there is no outbreak. Then, any randomised trial protocol in an emergency outbreak can be greatly simplified by reducing safety monitoring (e.g. collect only SAEs involving hospitalisation or death). Reliable previous safety studies can also simplify informed consent process.
- Previously agreed trial platforms and simple RCT protocols and expanded access protocols.\(^{13}\)
- Fieldwork can be simplified with clear and simple entry criteria, a concise informed consent form, expand use electronic devices and GCP compliant electronic data collection tools to simplify fieldwork, collection of minimal baseline data, simplified follow-up (e.g. blood spots may be used to archive blood with SAEs only hospitalisation/death); and use of non-trial outbreak-control data to detect EVD cases and time of onset, if feasible.

Observational studies during outbreaks would be useful especially for post authorization confirmation of efficacy. They are required by various regulatory pathways or to obtain additional information about vaccine performance. The same key needs described above apply to observational studies.

A collaborative approach to go further and faster

Under the leadership of the Ministry of Health of Uganda and with support from WHO and partners, the international community has demonstrated that we can collaborate to do it much faster with the country at the center, with ethics and regulatory approvals, with all issues being properly dealt with.

We have been able to go fast without cutting any corners. And we can do that even faster if we invest in the sort of the countermeasures platforms that we need for Sudan ebolavirus disease and the other pathogens that we have identified as being important.

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In addition to the elements noted above, faster initiation of studies includes having an a priori agreed legal framework (e.g. collaboration agreements) and insurance providing appropriate liability and compensation framework and, previously agreed funding and simplified process to access funds.

Strengthening collaboration between the experienced researchers in the countries at risk is very important, since we do not know where the next outbreak will occur.

WHO has a critical role to play in facilitating such collaborations. Other considerations include tools for good participatory practices and to address vaccine hesitancy.

**In recognition of the many experts and contributors who made it possible**

The Ministry of Health in Uganda and the Ugandan researchers: Prof Bruce Kirenga at Makerere University’s Lung Institute and Prof Pontiano Kaleebu at MRC Uganda whom with supported from WHO researchers, adjusted the protocols, trained about 200 researchers, and set up the equipment needed and the processes for the trial in record time.

The candidate vaccines developers and funders of cAd3 (Sabin Vaccine Institute and the US BARDA and NIH), cAdOx1 (Univ of Oxford, Jenner Institute, the UK government, and the Serum Institute of India) and rVSV SUVD (IAVI, MSD and US BARDA and NIH) produced, tested and put into vials in record time (79 days!) sufficient doses of the candidate vaccines for the trial and beyond. This is faster than what was achieved during the COVID pandemic.

Several global partners including Government of Canada, CEPI, European Union HERA and WHO allocated funds to facilitate the trial implementation. Others: Gavi, UNICEF, UKHSA, WT considered supporting it.

Scientists contributing to this expert consultation and the various expert committees including the WHO prioritization Committee, the Trial Steering Group and the DSMC and the hundreds of experts who supported all the research efforts.

The WHO colleagues in Uganda, the African Regional Office and Geneva.
Conclusions

In brief, the key conclusions from the meeting were:

**None of the candidate vaccines are currently suitable for use outside of a clinical trial**

It is critical to generate data to advance the evaluation of candidate vaccines in order to support future prioritization and possible future regulatory pathways towards an authorized or licensed product. These studies (including safety and immunogenicity, T cells, duration, modifiers of protection, heterologous regimens, cross protective responses in appropriate populations) can also be done in endemic regions which will yield important benefits likely including preparation for next steps.

**Prioritization of candidate vaccines is important**

Be it for entry into a ring trial during the next outbreak or as part of an observational study if clinical efficacy data is available and/or a regulatory authorization has been issued setting priorities among the various candidate vaccines is a key goal for the inter-outbreak period. Prioritization will be greatly facilitated if all vaccines are studied head-to-head in the same trial, and if the same qualified or validated assays are used to assess each vaccine. This does not preclude developers from organizing additional studies.

**Funded investigational vaccines already in internationally transferable vials is essential**

Having vialled candidate vaccines available and ready for international export/import at the start of the outbreak (in sufficient numbers for the trial and/or for deployment during the outbreak if efficacy data is available or emerges) is essential.

**Previously agreed trial platforms and simple pre-approved protocols are needed**

The design and pre-approval of simple trial protocols and faster regulatory and ethical approval processes is pivotal to ensure the prompt evaluation and deployment of any candidate vaccine. A ring vaccination trial, during an outbreak, similar to that performed in Guinea with rVSV ZEBOV-GP or ring vaccination as an observational study similar to that implemented in DRC (Expanded Access/Compassionate Use), will be the most reliable way to demonstrate vaccine efficacy.

**There are research teams in the countries at risk to conduct high quality research**

Anticipatory preparation of research teams in Uganda and other countries at risk and support for logistics and supplies can reduce the time between outbreak declaration and start of the studies. Moreover, there is political support and research capacity in Uganda and other countries at risk to carry out the studies discussed in a collaborative approach with vaccine developers, contributors, and local researchers, preferably in a collaborative way.

**A global framework to be able to initiate trials promptly without inappropriate deliberations on scientific issues by donors or recipients**

A previously agreed collaborative blueprint addressing legal framework and liability and insurance issues (to make sure that all investigators are covered, not just developers), and identifying flexible sources of funding to support rapid initiation of trial activities as part of outbreak response.