CEPI Scientific Advisory Committee (SAC) meeting summary

Date

Wednesday 26 July 2023

Location

Virtual

Attendees

SAC

- **Alash'le Abimiku,** International Research Center of Excellence, Institute of Human Virology, NG
- **Sani Aliyu,** Cambridge University Hospitals Foundation Trust, UK
- **Vineeta Bal,** Indian Institute of Science Education and Research, Pune, IN
- **Alan D. Barrett,** University of Texas, Medical Branch, US
- **Luciana Borio,** Arch Venture Partners, US
- **Paula Bryant,** National Institute of Allergy and Infectious Diseases, National Institutes of Health, US
- **Inger Damon,** Centers for Disease Control and Prevention/ Emory University, US
- **Michel De Wilde,** MDW Consultant, LLC, US
- **Christian Drosten,** Charité – Universitätsmedizin Berlin, DE
- **Azra Ghani,** Imperial College London, UK
- **Josie Golding,** Wellcome Trust, UK
- **Emmanuel Hanon,** Vicebio, BE (Chair)
- **Ken J. Ishii,** International Vaccine Design Center, The Institute of Medical Science, The University of Tokyo, JP
- **Kent Kester,** IAVI, US (Open session only)
- **Michael King,** University of Virginia, US (Vice-Chair)
- **Phil Krause,** WHO, US
- **Marc Lipsitch,** Harvard T.H. Chan School of Public Health, US
- **Dominique Maugeais,** RH Solutions, FR
- **Gary Nabel,** ModeX Therapeutics, US
- **Laura Palomares,** Instituto de Biotecnología, Universidad Nacional Autónoma de México, MX (Vice-Chair)
- **Peter Paradiso,** Paradiso Biologics Consulting, LLC, US
- **Stanley Plotkin,** University of Pennsylvania, US
- **Mahmudur Rahman,** GHD|EMPHNET, BD
- **Rino Rappuoli,** Fondazione Biotecnopolo di Siena, IT
- **Ana Maria Henao Restrepo,** WHO
- **Stephen Thomas,** SUNY Upstate Medical University, US
- **David Vaughn,** Bill & Melinda Gates Foundation, US
- **Linfa Wang,** Duke-NUS Medical School, SG

Apologies

- **Peter Dull,** Bill & Melinda Gates Foundation, US
- **George Gao,** Chinese Center for Disease Control and Prevention, CN
- **Rebecca Grais,** Pasteur Network, FR (Recused)
- **Krishna Mohan Vadrevu,** Bharat Biotech International, IN
- **Marco Safadi,** Santa Casa de Sao Paulo School of Medical Sciences, BR
- **Peter Smith,** London School of Hygiene & Tropical Medicine, UK

Invited guests

- **Ifedayo Adetifa,** Nigeria CDC
- **Tarik Mohammed,** Nigeria CDC
- **Sylvanus Okogbenin,** Irrua Specialist Teaching Hospital, Nigeria
- **Rosa Poetes,** McKinsey
- **Arthika Sripathy,** McKinsey

CEPI

- **Anand Ekambaram,** Executive Director, Manufacturing and Supply Chain
- **Raafat Fahim,** Consultant
- **Richard Hatchett,** CEO
- **Katrin Ramsauer,** Project Leader
- **Melanie Saville,** Executive Director, Research and Development

A number of additional CEPI staff also attended as observers.

IAVI team members

A number of IAVI staff attended to present their Phase I data.

Agenda

Time	Session	Participants
12:30-12:40	CLOSED SESSION: Welcome and objectives	SAC External invitees
12:40-14:20	CLOSED SESSION: Progressing the Lassa vaccine portfolio to advanced development	SAC External invitees
14:20-15:00	OPEN SESSION: IAVI: VSV Lassa Fever Vaccine Development Program	IAVI SAC External invitees
15:00-15:40	CLOSED SESSION: SAC discussion on IAVI data and plans	SAC External invitees
15:40-16:25	CLOSED SESSION: Line of Sight to Commercial Manufacture: Lassa as a test case for CEPI's Manufacturing Strategy	SAC External invitees
16:25-16:30	Summary and close	SAC External invitees

Executive summary

Objectives

A four-hour virtual SAC meeting was held on Wednesday 26 July 2023. The main objectives were to:

- provide a general overview of the Lassa programme, including the Target Product Profile (TPP) and current portfolio composition
- review the proposed strategy for broadening the portfolio in order to de-risk a late-stage candidate
- consider the suitability of a candidate to enter late-stage development
- evaluate CEPI's proposed LMIC commercial manufacturing strategy

It was highlighted that CEPI was not seeking a go/no-go decision for any one candidate but rather asking for scientific input on the proposed progression of the Lassa fever vaccine portfolio.

Advancing the development of CEPI's Lassa portfolio

- The SAC was supportive of CEPI expanding the portfolio to de-risk the portfolio, and was particularly interested in exploring mRNA and novel antigens in addition to existing partners
- The SAC discussed the value of different platforms in different scenarios
- The SAC felt that it is too soon to narrow CEPI's scope to preventive vaccines only as:
    - The current CEPI Target Product Characteristics (TPCs) allow for protection maintained by boosters, and experience with Ebola suggests that national authorities are unlikely to accept use of a vaccine as preventive if it will require re-administration in the event of an outbreak
    - Projected manufacturing capacity falls short of what would be required for a preventive campaign, particularly if booster doses are required.
- Several participants encouraged CEPI to consider broadening the TPCs with regard to immunogenicity to include cell-mediated immunity (particularly T cell response) as well as neutralising antibodies.

Plans for phase 2 trials and community and regulatory engagement

- A discussion was held around where Lassa primarily occurs, noting the large percentage of cases occurring in Nigeria. It will be important to plan where trials occur and the approach to regulatory approvals.
- Inclusion of pregnant women in phase 2 trials was seen as critical, with awardees' current plans involving them too late – Developmental and Reproductive Toxicology (DART) studies and early regulatory (and ethics committee) engagement were strongly recommended.
- It was reiterated that proactive risk communication will be paramount to ensure that endemic countries are well-informed about the vaccine upon availability.

Manufacturing strategy

- A discussion was held on the importance of data to plan for manufacturing activities, and to think through tech transfer and when this should occur

Introductions

The Lassa Fever programme constitutes CEPI's largest investment to date outside of COVID activities. As of 2023, there are several candidates moving rapidly towards field efficacy clinical trials and, as such, CEPI is keen to engage the SAC on a number of critical issues.

The main objectives of the meeting were to:

- provide a general overview of the Lassa programme, including the TPP and current portfolio composition
- review the proposed strategy for broadening the portfolio
- consider the suitability of a candidate to enter late-stage development
- evaluate CEPI's proposed LMIC commercial manufacturing strategy

CEPI was asking for scientific input on the proposed progression of the Lassa fever vaccine portfolio.

A particular welcome was also extended to the external invited guests who had been asked to join based on their specific Lassa Fever expertise:

Sylvanus Okogbenin is the Chief Medical Director for the Irrua specialist teaching hospital, a centre of excellence for management, control and research of Lassa fever in Nigeria. He was recently appointed as Chair of the Institute for Viral Haemorrhagic Fevers and Emergent Pathogens, and has a particular interest in Lassa fever in pregnant women – a particularly vulnerable group with high mortality and morbidity.

Ifedayo Adetifa is the Director General of the Nigerian Centre for Disease Control and Prevention. He is an infectious disease epidemiologist with a focus on vaccine epidemiology.

ITEM 1: Advancing the development of CEPI's Lassa portfolio

When CEPI made its original investment into six Lassa vaccine candidates, its end goal was to successfully deliver at least one through early clinical development and into stockpile for use in an outbreak. However, substantial improvements in the generation of epidemiological data over the last few years have caused CEPI to reconsider its position. Data have shown that Lassa is very much a seasonal disease, with active seasons from December to April, and is also predominantly zoonotic, with minimal human-to-human transmission. In light of this, CEPI believes that targeting preventive vaccination may be a more appropriate strategy, and so is now working towards a fully licensed vaccine and beginning to prepare for clinical efficacy trials in affected countries. Of note, the WHO TPP that was developed as part of the R&D Blueprint efforts around Lassa fever included both preventive and reactive strategies.

CEPI is also committed to playing a role in building the infrastructure that will enable research and implementation of a vaccine in endemic regions, and so continues to fund a variety of enabling activities in parallel, including:

- a clinical trial site readiness programme in West Africa which will, amongst other things, involve working closely with in-country partners to develop fit-for-purpose trial protocols
- support for the definition of biomarkers
- development of a CMC framework to support LMIC manufacturing, and
- the ECOWAS-RegECs regulatory programme funded by EDCTP which aims to align clinical trial applications with stringent regulatory authority standards.

Portfolio overview

CEPI's target product characteristics (TPCs – based on the WHO TPP), are as follows:

- Safe and effective prevention of Lassa Fever disease (all lineages)
    - Safety and reactogenicity comparable to WHO recommended routine vaccines
    - Immunogenicity demonstrated by induction of neutralizing antibody response

- Appropriate for use in all populations including children, pregnant women, and people living with HIV
- Appropriate for use in routine preventive vaccination campaigns
- Injectable using standard volumes and routes
- Storage at 2-8°C (preferred)

There are currently four vaccine candidates in CEPI's Lassa fever vaccine portfolio; two clinical and two pre-clinical. All four candidates use the same antigen – the glycoprotein C precursor from the Josiah strain (clade IV).

The three most advanced candidates are viral vector-based vaccines, with two of the rVSV programmes being built on platforms similar to Merck's Ervebo, which is known to have a favourable reactogenicity profile including in children and pregnant women. The third viral vector candidate uses the ChAdOx1 platform which has the positive characteristics of there already being a well-defined safety profile and demonstrated success in manufacturing at large and commercial scales.

The final candidate is an mRNA-based vaccine. This programme has the benefit of building up mRNA vaccine capacity within both the developer and the antigen but will also feed directly into CEPI's vaccine library programme.

Additional activities that CEPI is considering (and in some cases already pursuing) include:
- expanding the portfolio by a) actively adding candidates and b) networking with other developers or funders
- including arenaviruses in the vaccine library programme, in which CEPI is attempting to identify antigens that could be common to a virus family, and then create exemplar vaccines for use in outbreak setting
- investigating the protective capacity of antibodies, T cells and other immune mediators, to help accelerate the development of any new and next generation candidates
- developing a centralized laboratory network to enable information and capacity sharing.

The critical questions that CEPI asked of the SAC were as follows:
- What is the SAC's opinion on the current portfolio?
- Is the current portfolio sufficient to de-risk a lead candidate as it moves into Phase II and III trials?
    - What are the main gaps?
- Does the SAC agree with CEPI's updated strategy to develop a preventative rather than reactive vaccine?

Key points in the discussion

How cost of goods are factored into the CEPI TPCs was raised, noting that the rVSV candidate is based on the same platform as an Ebola vaccine. It was noted that the developer, in collaboration with a CDMO, has developed a more efficient, optimized manufacturing process to help deliver relatively lower cost of goods; however, the price will be contingent on final dose selection and production scale.

The role of pre-existing anti-vector immunity in the target population and the impact of future clinical trials was raised. It was noted that efforts are ongoing, but this was not expected to be an issue/to cause issues.

A discussion around dose finding was held, and CEPI Management noted that some dose finding was done in phase 1, but that this will be further refined in phase 2a.

Regarding CEPI's current portfolio:

- Including mRNA in the portfolio was noted as positive. It is hoped that the inclusion of multiple antigens in the mRNA vaccine will broaden the immune response.

- CEPI might add cell mediated immunity to the TPC moving forward (which is included in the WHO TPP).
- There is no single candidate that is both single dose and has the thermostability set out in the TPCs. This should inform CEPI's work with existing partners, and potential future investments.
- It was noted that there are two rVSV candidates, and CEPI is actively reviewing data of both to inform how it progresses the portfolio.
- It was noted that the portfolio and individual candidates can be viewed to have risks, as is common with vaccine development.

Overall, the SAC agreed that there would be benefit in CEPI expanding its portfolio based on the known probability of success of these types of programmes.

The SAC was generally supportive of investigating novel antigens.

The approach to a preventative or reactive vaccine

Although the epidemiological data suggest that a preventive vaccine would be most effective, the SAC felt that it is too soon to narrow CEPI's scope:

- doing so would put pressure on a lead candidate to achieve a level of broadness and duration of protection that is not yet guaranteed.
- there may be value in having both preventive and reactive candidates in the portfolio.
- categorising the vaccine either way at this point will not change the approach to efficacy trials
- the CEPI TPC allows for protection maintained by boosters, but WHO's experience with Ebola suggests that national authorities are unlikely to accept use of a vaccine as preventive if it will require re-administration in the event of an outbreak.
- projected manufacturing capacity falls short of what would be required for a preventive campaign, particularly if booster doses are required.

ITEM 2: Plans for phase 2 trials and community and regulatory engagement

It is important that CEPI balances its investment approach across the portfolio and ensures all necessary stakeholders are engaged in the finalising of trial protocols for Lassa Fever.

CEPI should consider the equity impact of plans to have more advanced PhII analysis done outside of Nigeria, and the importance of capacity building. It was noted that CEPI has issued a site readiness request for proposals which would support a breadth of sites.

It is important to have an inclusive design, including pregnant women and it was suggested that conducting DART studies and engaging with national regulatory authorities as early as possible would be beneficial and help to facilitate regulatory approval.

There are lessons to be learned from the COVID-19 vaccine roll out, with regards to community engagement, how to manage safety concerns, and ensuring support for vaccination.

In addition to the work of the ENABLE study, it was suggested more proactive search for cases could be helpful, e.g., a simple temperature check every two weeks may help to identify some of the milder cases which ordinarily may be missed.

ITEM 3: Manufacturing strategy

The current priorities for the CEPI Lassa programme from a manufacturing perspective are:

- to establish timelines for technology transfer to a LMIC facility, and

- to mitigate any risks associated with this transfer by supporting the facility to advance their capabilities.

The strategy for achieving these goals is being collaboratively developed by CEPI, the CDMO and the rVSV developer, with additional guidance sought from AVAREF and other national regulatory agencies. Mindful that the manufacturing strategy will be dependent on demand, CEPI has also commissioned a demand assessment for Lassa.

Thermostability

The SAC discussed thermostability, and the ideal temperature for vaccines, noting some would require specific efforts to have a formulation at 2-8ºC.

Clarification questions and general comments

A discussion was held on the manufacture location in the short and longer term, and the need to balance speed and ensuring consistency of material.

Does the SAC agree that a parallel manufacturing option is a prudent approach?

SAC members would be pleased to see a Lassa vaccine ultimately manufactured by an LMIC manufacturer but agreed that having a parallel track to minimise risk makes sense.

Does the SAC have any comments regarding the introduction of a 2-8ºC formulation?

It was noted that although a 2-8ºC formulation would of course be preferable, there are recent examples of up to 320,000 people being successfully vaccinated with a -80ºC formulation in equally challenging settings. As such, some SAC members felt that efforts to develop the 2-8ºC formulation could be a distraction at this point in time, given the other programme challenges still to be resolved.

The importance of not making later changes to the formulation given the additional clinical studies that may be needed was noted.