CEPI SAC Monkeypox meeting summary

Date	Time	Location
Friday, 29 July 2022	13:30-15:00 BST	Virtual

SAC attendees

Speaking/Chairing

- **Emmanuel Hanon,** Viome, BE (Chair)
- **Laura A. Palomares Aguilera,** Instituto de Biotecnología, Universidad Nacional Autónoma de México, MX (Vice-Chair)
- **Michael King,** University of Virginia, US (Vice-Chair)
- **Inger Damon,** Centers for Disease Control and Prevention, US
- **Ken J. Ishii,** International Vaccine Design Center, The Institute of Medical Science, The University of Tokyo, JP

Participating

- **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
- **Michel De Wilde,** MDW Consultant, LLC, US
- **Peter Dull,** Bill & Melinda Gates Foundation, US
- **Josie Golding,** Wellcome Trust, IE
- **Rebecca Grais,** Epicentre, FR
- **Kent Kester,** IAVI, US
- **Phil Krause,** WHO, US
- **Vasee Moorthy,** WHO, UK
- **Gary Nabel,** ModeX Therapeutics, US
- **Peter Paradiso,** Paradiso Biologics Consulting, LLC, US
- **Stanley Plotkin,** University of Pennsylvania, US
- **Mahmudur Rahman,** GHD|EMPHNET, BD
- **Rino Rappuoli,** GSK Vaccines, IT
- **Marco Safadi,** Santa Casa de Sao Paulo School of Medical Sciences, BR
- **Peter Smith,** London School of Hygiene & Tropical Medicine, UK
- **Krishna Mohan Vadrevu,** Bharat Biotech International, IN
- **Linfa Wang,** Duke-NUS Medical School, SG

Apologies

- **Alash'le Abimiku,** International Research Center of Excellence, Institute of Human Virology, NG
- **Paula Bryant,** National Institute of Allergy and Infectious Diseases, National Institutes of Health, US
- **Christian Drosten,** Charité – Universitätsmedizin Berlin, DE
- **George Gao,** Chinese Center for Disease Control and Prevention, CN
- **Azra Ghani,** Imperial College London, UK
- **Marc Lipsitch,** Harvard T.H. Chan School of Public Health, US
- **Dominique Maugeais,** Independent consultant, FR
- **Frances Priddy,** Moderna, US
- **Stephen Thomas,** SUNY Upstate Medical University, US
- **Michael Watson,** MEVOX & VaxEquity Ltd, US

CEPI attendees

Speaking

- **Richard Hatchett,** CEO
- **Melanie Saville,** Executive Director, Research and Development

Observing

- **Mike Aviles,** IT Officer
- **Valentina Bernasconi,** Head of Laboratory Science
- **Tiana Carstairs,** Project Manager
- **Danielle Craig,** Regulatory Affairs Lead, Americas
- **Arminder Deol,** Senior Scientist, Epidemiology
- **Sarah Doyle,** SAC and JCG Officer
- **Rebecca Farkas,** Head of Technology
- **Roice Fulton,** Consultant
- **Adam Hacker,** Director and Global Head of Regulatory Affairs
- **Renske Hesselink,** Senior Scientist, Chemistry Manufacture Controls
- **Nicole Lurie,** Executive Director, Preparedness & Response
- **Khadimul Mazhar,** Scientist - Epidemiology
- **Marion Motari,** Legal Counsel
- **Barbara Ngouyombo,** Senior Manager, Strategic Partnerships
- **Ranna Eardley-Patel,** Sustainable Manufacturing Lead
- **Mark Polhemus,** Disease Portfolio Project Leader
- **Sheldon Poujade,** Business Development Lead
- **Jodie Rogers,** Communications Manager
- **Kelly Simpson,** Portfolio Officer
- **Nadia Tornieporth,** Consultant

Guests

- **Lorna Leal Alexander,** EMA
- **Steven Anderson,** FDA
- **Doran Fink,** FDA
- **Richard Forshee,** FDA
- **Chad Irwin,** Health Canada
- **Peter Marks,** FDA
- **Ana Maria Henao Restrepo,** WHO
- **Dean Smith,** Health Canada

Richard opened the meeting, welcomed attendees, and passed over to Manu to give an overview of the agenda and objective for the session, which was to identify evidence gaps to be filled with regards to monkeypox vaccines, and align on the role that CEPI should play in this.

Some members made a declaration of interest, but all were deemed not to be relevant for this meeting.

Melanie then began the main session by acknowledging everyone's awareness of the WHO declaration of Monkeypox as a Public Health Emergency of International Concern (PHEIC) on 23 July 2022.

She provided a brief overview of currently licensed products, as follows:

- The Bavarian Nordic (BN) non-replicating MVA vaccine is now licensed in 3 regions (accurate as of 29 July 2022) under the brand names Jynneos (US – September 2019), Imvamune (Canada – November 2020) and Imvanex (EU – July 2022).
    - The US already has a stockpile of 16 million doses in bulk, and 1 million in drug product, and BN are in discussion with multiple other countries regarding manufacturing and supply; however, notably, none of these are within Africa.
- Japan has developed a replicating attenuated vaccine and currently has a stockpile of 126 million doses.
    - In contrast to BN, Japan has expressed a desire to liaise collaborate with GAVI and WHO for any international use, rather than individual countries.

It was noted that fill & finish capacity, and the need for a bifurcated needle with the Japanese vaccine may make deployment at scale challenging, and that all Monkeypox indications have been obtained without efficacy trials, and are instead based on animal trials and human immunogenicity data.

Lastly, Melanie advised the group that CEPI has already made some small investments (375K USD) in the development of both assays and antibody research reagents for Monkeypox through implementing partners, NIBSC and UKHSA, as encouraged by members of the JCG during a meeting held 6 weeks prior.

CDC perspective

Inger Damon, Director, Division of High Consequence Pathogens and Pathology, CDC

Inger began by voicing her opinion that now is an extraordinary and critical time to be collecting real-world data on vaccine efficacy against Monkeypox due to a) the high incidence of per-mucosal transmission in the current outbreak, and b) the administration of single dose regimens that we are seeing in many countries:

a) Historical clinical trials investigating efficacy of the BN vaccine showed that there was a reduction in vaccinia virus replication; however, 25-30% of individuals still had some replication at the lesion site. As much of the Monkeypox transmission we are seeing in the current outbreak is through direct exposure to a per-mucosal surface, collection of real-world data on efficacy of the vaccines against mucosal transmission will be critical.
b) The BN vaccine is a two-dose regimen, administered 28 days apart; however, some countries are administering single doses, with boosters either delayed or not delivered at all. If single doses elicit a sufficient immune response, this could present the opportunity to employ dose sparing regimens more broadly which could help to minimise the impact of current supply shortages. So far, some limited data based on intradermal administration with 10^7 particles has demonstrated equivalent immune response. This would likely still need to be administered as part of a two-dose series, but the BN vaccine would be used as a prime, and then followed by a replicative vaccinia virus vaccine booster – a potential application for LC16M8.

Alan Barrett asked whether one dose of vaccine protected against Monkeypox in animal models, to which Inger responded that studies investigating the BN vaccine had shown that a single dose provided 85% protection against death, but with some rash lesion development. This was done using the Congo basin lineage of the virus.

Finally, Inger commented that contact tracing has been a challenge, and therefore development of a Monkeypox-specific serologic assay may soon become critical. A Monkeypox serologic signature that is distinct from the vaccinia virus may also help to further identify vaccine effectiveness as we will be able to gain greater visibility over whether those who have been vaccinated are being boosted by direct Monkeypox exposure. So far, nothing has made it to commercialisation, although a CLIA assay has been validated internally at the CDC, allowing for very limited capacity serologic testing.

In response to this, Gary Nabel asked whether Inger had confidence in the current assay that is being used, and to confirm whether it is scalable, given the increasing demand for testing.
Inger explained that the current US assay (developed between 2000-2003) is a PCR-based assay that looks for nucleic acid within a highly conserved gene of the virus, and that will detect vaccinia virus, monkeypox and cow pox. As replicating vaccinia virus that would be detected by the assay is not currently being used the US, they have decided they are comfortable that this assay can be effectively used to diagnose Monkeypox in context of the current outbreak. Due to Monkeypox having a viraemic stage of disease, DNA can be detected in the serum; however, the richest source of information is the lesions themselves. Accurate testing can be done with an external swab of a lesion, although the most reliable approach would be to test internal contents.
Testing capacity through commercial labs is now approximately 80k tests per week, but the US is currently only using about 5% of this.

Richard Hatchett also asked whether we are currently seeing Monkeypox infections in age groups that we would expect to have been vaccinated against smallpox, to which Inger responded that we are, and that this further compounds the need to explore per-mucosal transmission.

Japanese vaccines

Ken J. Ishii, Professor and Director, International Vaccine Design Center, University of Tokyo

Ken Ishii presented a brief overview of the 2013 WHO safety and efficacy grade tables of second and third generation smallpox vaccines (ACAM2000, LC16M8 – the strain on which the Japanese vaccine is based, and MVA – the strain on which the Bavarian Nordic vaccine is based). He highlighted that ACAM2000 and LC16M8 demonstrated superior efficacy compared with MVA, with LC16M8 also having a more favourable safety profile to the other two. As such, in 2014, WHO stated that ACAM2000 and LC16M8 would be preferable for stockpiling purposes. LC16M8 was licensed in Japan in 1975, is currently stockpiled against bioterror threats and, as of 29 July 2022, is now indicated for use against Monkeypox.

WHO perspective

Ana Maria Henao Restrepo, Co-Lead R&D Blueprint for epidemics, WHO Health Emergencies programme

Ana Maria Henao advised that, alongside the announcement of Monkeypox as a PHEIC, WHO also issued several recommendations to member states in an effort to co-ordinate any work to fill remaining research gaps related to Monkeypox vaccines.

She congratulated our Japanese colleagues on the licensure of LC16M8 and informed the group that WHO is in the process of requesting and analysing critical data on LC16M8, to enable them to release an official position on the vaccine. WHO then intends to support with the generation of clinical evidence that will be important for facilitating global policy changes, and is in conversation with the Japanese Government, developers and multiple other global stakeholders regarding how to expand production of the LC16M8 vaccine and ensure equitable access.

Regarding the MVA vaccines, Ana Maria advised that WHO is working on how to generate randomised evidence, but wanted to be clear that generation of these data will not delay the deployment of vaccines.

She later added that WHO is proposing two avenues:

1. Testing vaccines in countries with zoonotic transmission: WHO is interested in both the Japanese and MVA vaccines in this context; however, Ana Maria advised that BN have said they cannot provide vaccines for testing in these populations until 2023.
2. Working on TPPs: Ana Maria advised the group that the TPP for therapeutics has already been defined, and that WHO is now developing the TPP for vaccines. She stated that support for this activity would be very welcome.

WHO is due to convene on 2 August 2022 to discuss randomised evidence methods, observational studies, how to work together to address challenges associated with case control and cohort studies, and use of platform databases for evaluation of these vaccines. A global research and innovation forum meeting will follow on 11 August 2022.

Regulatory perspective

Peter Marks, Director, Center for Biologics Evaluation and Research (CBER), FDA

Peter Marks recapped the current situation in the US, reminding the group that there is currently only one licensed vaccine (Jynneos) but that an additional stockpile of ACAM2000 also exists.
He reiterated that there are high levels of uncertainty around the efficacy of Jynneos in the real world, given that all data so far are inferential, based on animal lethal challenge models, and in line with this restated the importance of collecting real-world data. However, he highlighted concerns that the health system in the US is so stretched that coordinating large-scale randomised controlled trials may not be feasible.

In response to this, Gary Nabel asked whether there had been any consideration of using ring vaccination in the context of a controlled clinical trial, noting that this might place less strain on the health system, but still help to answer many of the questions regarding vaccine effectiveness in preventing transmission, and efficacy of single dose regimens.
Peter replied that this might indeed be possible in terms of scale, but referred back to Inger's point regarding the difficulties of contact tracing, particularly in the currently affected population, which has led to the US' current approach of 'post-exposure prophylaxis ++', an incredibly wide ring of vaccination around the infected individual.

With Peter's comment in mind regarding health system capacity for large-scale trials, Ana Maria also proposed an alternative approach to collecting randomised data, using the UK as an illustrative example:

- At present, the UK has 40k high-risk people eligible for vaccination but only 20k doses. As such, nurses or public health officers currently have the responsibility for choosing who within the at-risk population should get vaccinated first. Ana Maria suggested that a better approach would be to remove this decision from the nurse and entirely randomise the list instead, but acknowledged that it would take courage for a public health agency to agree to do this.

There was a large amount of support from the group for this approach, which was agreed to be a very fair way to ensure that those with equal eligibility for the vaccine have an equal chance of getting it, an effective way to generate valuable data, and an opportunity to 'make lemonade from the lemons of supply shortage'.
As a critical first step, Gary suggested that biostatisticians be engaged to help identify what sample size would be needed, what the endpoints should be, and therefore whether this will be a viable approach.

Are additional vaccines needed or are existing candidates sufficient?

Overall, the group was confident that, despite only having inferential data, current vaccines will be sufficiently effective against Monkeypox, and they felt that there is neither the time nor need to develop a new vaccine to address the current outbreak. There are clear limitations of currently available vaccines in that we do not know the level of protection that a single dose offers, and the protection that is offered against per-mucosal transmission; however, the advisors were quite clear that assessment of these factors, although critical, needs to be secondary to efforts to enable access.

Nonetheless, Stanley Plotkin highlighted that there is a known East African Monkeypox strain that causes more serious disease and has not previously been used in vaccine development, and so strongly recommended that efficacy of current vaccines against this strain is investigated.
He also expressed surprise that there was no representation from Fort Detrick, where JW Hooper is currently investigating a DNA-based vaccine, an approach Stanley said he perceived to be the best work thus far on Monkeypox. He strongly urged CEPI to consider funding this research.
Manu commented that he was also impressed by what he had seen from this group but suggested that such investments may be a lower priority as they are unlikely to have a short-term application in the current outbreak.

Recommendation: CEPI to arrange meeting with JW Hooper of Fort Detrick to discuss potential funding of ongoing research into DNA-based Monkeypox vaccines.

Given concern about high titre mucosal exposures and the uncertainty of single dose efficacy of a non-replicating vaccine, Richard Hatchett considered whether early testing of combined T-pox/MVA post-exposure prophylaxis might be warranted, as, if we go through a normal trial procedure it might take time to realise that one dose vaccination against high titre mucosal exposures is not effective.

Conclusions

Manu concluded the meeting by summarising the key points from the session:

1. **Begin by facilitating equitable access** – There was general consensus that current vaccines will be sufficiently effective against Monkeypox and there is neither the time nor need to develop a new vaccine to address the current outbreak. Generation of efficacy data should not delay deployment and the primary focus should be on enabling equitable access in order to minimise illness and death.
    - Mike King suggested that CEPI should leverage its COVAX experience to ensure a global rather than nationalistic response.
    - Appropriate allocation of the stockpile of the newly licensed Japanese LC16M8 vaccine, and resolution of manufacturing capacity bottlenecks that are causing supply shortages, will play crucial roles in achieving this.
    - WHO is in the process of liaising with the Japanese Government regarding allocation of the LC16M8 stockpile.

2. **Generate real-world evidence**
    - **Dosing**: Given many countries are already administering single doses of the BN vaccine, it was agreed that it will be critical to understand the comparative efficacy of single vs two-dose regimens in preventing severe disease. If single doses illicit a sufficient immune response, this could present the opportunity to employ dose sparing regimens more broadly which could also help to minimise the impact of current supply shortages.
    - **Preventing transmission**: Given the high incidence of per-mucosal transmission, and the knowledge that 25-30% of individuals in previous trials still had some replication at the lesion site, efficacy of the vaccines against per-mucosal transmission will also be a priority.
    - **Methodology**: Health systems are already stretched, making initiation of large-scale randomised trials potentially difficult. Ring vaccination trials were recommended as an alternative, noting that these might place less strain on health systems; however, many advisors flagged that contact tracing in the target population is extremely challenging. There was huge support for Ana Maria's proposed alternative approach to collecting randomised data, which was agreed to be a very fair way to ensure that those with equal eligibility for the vaccine have an equal chance of getting it. Ultimately, the advisors agreed that a combined approach employing all of these study designs would likely be necessary.