CEPI SAC meeting summary

Date

Wednesday 26 – Thursday 27 April 2023

Location

Oslo

SAC attendees

Speaking/Chairing

- **Emmanuel Hanon,** Vicebio, BE (Chair)
- **Michel De Wilde,** MDW Consultant, LLC, US

Participating

- **Alash'le Abimiku,** International Research Center of Excellence, Institute of Human Virology, NG
- **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 (Virtual)
- **Inger Damon,** Centers for Disease Control and Prevention/ Emory University, US
- **Christian Drosten,** Charité – Universitätsmedizin Berlin, DE
- **George Gao,** Chinese Center for Disease Control and Prevention, CN
- **Nathalie Garcon,** Independent consultant (Guest)
- **Azra Ghani,** Imperial College London, UK
- **Josie Golding,** Wellcome Trust, UK
- **Rebecca Grais,** Pasteur Network, FR
- **Ken J. Ishii,** International Vaccine Design Center, The Institute of Medical Science, The University of Tokyo, JP
- **Kent Kester,** IAVI, US
- **Michael King,** University of Virginia, US (Vice-Chair) (Virtual)
- **Phil Krause,** WHO, US
- **Dominique Maugeais,** RH Solutions, FR
- **Krishna Mohan Vadrevu,** Bharat Biotech International, IN (Virtual)
- **Stanley Plotkin,** University of Pennsylvania, US
- **Mahmudur Rahman,** GHD|EMPHNET, BD
- **Peter Smith,** London School of Hygiene & Tropical Medicine, UK
- **Stephen Thomas,** SUNY Upstate Medical University, US (Virtual)
- **David Vaughn,** Bill & Melinda Gates Foundation, US
- **Linfa Wang,** Duke-NUS Medical School, SG

Apologies

- **Sani Aliyu,** Cambridge University Hospitals Foundation Trust, UK
- **Vineeta Bal,** Indian Institute of Science Education and Research, Pune, IN
- **Peter Dull,** Bill & Melinda Gates Foundation, US
- **Marc Lipsitch,** Harvard T.H. Chan School of Public Health, US
- **Vasee Moorthy,** WHO, UK
- **Gary Nabel,** ModeX Therapeutics, US
- **Laura A. Palomares Aguilera,** Instituto de Biotecnología, Universidad Nacional Autónoma de México, MX (Vice-Chair)
- **Peter Paradiso,** Paradiso Biologics Consulting, LLC, US
- **Rino Rappuoli,** GSK Vaccines, IT
- **Marco Safadi,** Santa Casa de Sao Paulo School of Medical Sciences, BR

CEPI attendees

Speaking/Chairing

- **Nadia Cohen,** Project Leader
- **Christine Dahlke,** Translational Immunology Lead
- **Matthew Downham,** Director, Manufacturing and Supply Chain Network
- **Ranna Eardley-Patel,** Sustainable Manufacturing Lead
- **Anand Ekambaram,** Executive Director, Manufacturing and Supply Chain
- **Daniel Fullen,** Senior Manager - Technology
- **Ingrid Kromann,** Director, Manufacturing and QC Development
- **Richard Hatchett,** CEO
- **Diletta Magini,** Sustainable Manufacturing Lead
- **Melanie Saville,** Executive Director, Research and Development
- **Christof Vinnemeier,** Clinical Development Operations Lead
- **Gerald Voss,** Consultant
- **Stacey Wooden,** Technology Lead

Supporting

- **Mike Aviles,** IT Officer
- **Sarah Doyle,** SAC and JCG Officer
- **Roice Fulton,** Consultant
- **Inga Hanstveit,** CEO Front Office and Events Coordinator
- **Nigel Mellor,** IT Officer
- **Sheldon Poujade,** Business Development Lead
- **Ashley Tsai,** Portfolio Officer
- **Claire Willman,** Deputy Chief of Staff
- **Holly Wingfield,** Private Secretary

PSMB

- **Luc Debruyne,** PSMB Chair

A number of additional CEPI staff attended as observers, both in person and virtually.

Agenda

Time	Session		
10:30–11:00	**Welcome and objectives** *Manu Hanon*		
11:00–12:30	**Critical landscape developments** *Manu Hanon, Melanie Saville, Michel De Wilde*		
12:30–13:30	**Lunch**		
13:30–14:30	**Manufacturing strategy intro** *Anand Ekambaram*		
14:30–14:45	**Break**		
14:45–15:45	**1. Manufacturing technology roadmap** *Ingrid Kromann and Ranna Eardley-Patel*	**2. Manufacturing network and sustainability** *Matthew Downham and Diletta Magini*	**3. Clinical preparedness** *Christof Vinnemeier*
15:45–16:45	**Breakout group playback summaries**		
16:45–17:00	**Summary and close** *Manu Hanon*		

Time	Session	
09:00–09:15	**Welcome and day 1 recap** *Manu Hanon*	
09:15–10:00	**H5N1** *Melanie Saville*	
10:00–11:15	**Managing the BPCV portfolio** *Nadia Cohen*	
11:15–11:30	**Break**	
11:30–12:00	**CfPs in development (intro)**	
12:00–13:00	**a. Adjuvants** *Dan Fullen*	**b. Broadly protective filovirus vaccine** *Gerald Voss*
13:00–13:45	**Lunch**	
13:45–14:45	**c. mAbs** *Stacey Wooden*	**d. Mucosal immunity and CHIM** *Christine Dahlke*
14:45–15:45	**CfPs in development (playback summaries)** *Manu Hanon*	
15:45–16:00	**Summary and close** *Manu Hanon*	

Day 1

ITEM 1: Critical landscape developments (Plenary)

Led by: Manu Hanon, Melanie Saville and Michel De Wilde

Ahead of the April 2023 SAC meeting, CEPI took the decision to introduce a new, SAC-led agenda item during which members could volunteer to present on critical developments of their choice in the vaccine landscape. The objective of this session was to stimulate discussion on innovations that CEPI may not have line of sight on or currently be investing in, and/or which the SAC feel could be critical for helping to deliver on CEPI's mission.

Manu Hanon opened the session by giving a comprehensive overview of recent innovations related to vaccine platforms – given their pivotal role in the response to the COVID-19 pandemic - and providing his thoughts on the implications for CEPI.

What's new re vaccine platforms and what are the implications for CEPI?

Similar to the evolution of species, innovation in vaccinology is often driven by external pressures. In evolution these pressures may be changes in availability of habitat or food, whereas in vaccinology, the pressures come in the form of outbreaks. Explosions in innovation were particularly seen around smallpox in the early 1900s, H1N1 in 2009, and most recently, COVID-19 in 2020.

The H1N1 pandemic drove two important innovations which are still used and impactful on the field today: firstly, the use of high doses of influenza haemagglutinin (>50 micrograms) to improve the efficacy of flu vaccines, something which has become the standard of care now in seasonal vaccines – and secondly, the use of adjuvants, allowing developers to both decrease the amount of antigen within a vaccine, and introduce broad immune protection (evidenced by neutralising antibodies).

COVID has also pushed ahead a set of new technologies. However, it is important to note that monoclonal antibodies, viral vectors and mRNA were all in existence before the pandemic – although they were not perceived to be transformational in quite the same way they are now. In this case, the pandemic has 'revealed' their potential, demonstrating the importance of preparedness in pandemic response – previous investigation into how to rapidly develop cancer vaccines enabled application of this speed research to an infectious diseases context, and standardization to be established.

In addition to platform advancements, increased understanding of structural vaccinology has also played a huge role in the success of the pandemic response; it is not enough to have identified the right antigen, there is also the need to also ensure it is in the right conformation. We now know that COVID-19 vaccines locked in pre-fusion form give best immune response, and data generated by Moderna, GSK and Pfizer on RSV vaccines also support the importance of getting the right conformation to have an effective RSV vaccine.

Overall, CEPI and other development companies have a bigger 'toolbox' than ever before, which while exciting, also presents the problem of prioritisation:

Firstly, who should we partner with?

Are classical vaccine manufacturers going to be disrupted and disappear?

> If we look at the vaccines currently part of the US recommended immunization schedule, it is clear that the new technologies emerging will not be applicable across the board, and as such, we are more likely to a diversification of the vaccine landscape than a compression; classical developers will still have their place.

Are newcomers sustainable?

> New developers often have smaller portfolios of commercial vaccines, but it is likely that their technologies will have applications beyond COVID-19 (for example, Moderna's results on RSV are very positive).

Secondly, what are the upcoming battles in the field of vaccinology?
Manu highlighted four critical areas:

- High efficacy and multivalent respiratory virus vaccines
- New therapeutic cancer vaccines (which could help to inform manufacturing geodiversification strategies based on their highly decentralized development in small units)
- Manufacturing speed and innovation
- mAbs for infectious diseases

There are also four main ways in which companies compete in the vaccine space:

- Striving to develop a better performing vaccine – this could lead to a battle between adjuvanted subunit and mRNA vaccines
- Playing the numbers game – increasing the number of valences in a vaccine in order to achieve broader protection
- Playing the convenience game – improving access and uptake by reducing reactogenicity, delivering thermostability, and developing needle free/alternative routes of administration
- Playing the manufacturing speed game – producing vaccines faster for use in the context of pandemics, seasonal flu, and personalised cancer vaccines

All of these factors have the potential to impact CEPI's strategy moving forward. So, what should CEPI do? Manu's recommendation was to apply learnings from the pandemic, and in particular, recognise and build on the value of standardized platforms. He suggested that classical technologies, for example adjuvants or CHO production, could be further 'platformized' in order to achieve faster responses in the future. He also recommended continuing to advance new technologies such as mRNA, drive innovation in antigen design through broadly protective programmes, and innovate in the manufacturing space (focusing on greater simplicity and yield) in order to drive better access and lower cost of goods.

Lastly, he encouraged CEPI to consider what challenges might lay ahead outside of the world of viruses, and questioned whether CEPI could or should play a role in finding optimal modalities for bacterial or fungal diseases, noting that existing platforms will likely not be compatible.

Discussion

Stanley Plotkin was in agreement with Manu's recommendations, but added that one critical development had been missed in his mind. As many of the outbreak viruses we are presently encountering are mucosal pathogens, he suggested that the field of vaccinology needs to prioritise determining how to induce better mucosal responses. He highlighted that the RSV vaccines currently in development each give incomplete protection, and his view was that this is because they do not do on the mucosal surface what they do in the serum.

Ken Ishii also made an addition to Manu's list, advising strongly that protective immune memory should be a priority. Following the COVID pandemic, people are getting very tired of having to have repeat doses year on year, and he questioned whether these types of regimens do in fact count as true vaccines as opposed to 'immuno-prophylaxis'. Manu agreed, but noted that often the need for repeat doses driven by changes in the antigen rather than waning protection, and that research into immune memory should be balanced with research into how to achieve broad protection.

Phil Krause also felt that improved durability would be critical for the success of vaccines against CEPI core pathogens, but suggested that it may be a less important factor in the context of the 100 days mission. As such, he urged CEPI to be clear on its priorities, commenting that it will not be possible to achieve everything. Similarly, he felt that there may be conflict between CEPI's 100 day and vaccine equity goals, and that an attempt to achieve both may result in achieving neither.
Richard Hatchett disagreed that the 100 days mission and vaccine equity are in conflict, and suggested that they are in fact tightly linked in a pandemic context: The biggest driver of inequity is often scarcity, and so

the faster you can scale a vaccine, the faster you can eliminate the scarcity and address (in part) the equity problems.
With regard to CEPI's priority pathogens, Richard acknowledged that the 100 days mission activities may not always be relevant or applicable (e.g. the vaccine that is ultimately needed for Lassa may not be one that is delivered on a rapid response platform), but commented that he didn't think there was an inherent trade-off or 'zero sum game' given the value-add of accelerating vaccine development in general. Phil acknowledged these points, agreeing that there would not always be tension, but nonetheless advised that CEPI will need to decide which factor or programme to prioritise when there is.

Azra Ghani added that a drive to increase vaccine equity will also (need to) contribute to shaping markets. Whilst she agreed that respiratory vaccines are important based on the perspective we have now of pandemics, if the intention is to increase geographical diversity in R&D&M, then supporting the development of measures against more localised health problems may need to become a priority over global respiratory threats.

Lastly, Michel De Wilde commented that the difference in speed between mRNA and subunit vaccines may have been amplified during SARS-CoV-2 and may not be totally representative.

CEPI 2.0 and the 100 days mission

Next, Melanie Saville briefly reminded the group of the CEPI 2.0 plan which is based around three core pillars:

- Prepare – During CEPI 1.0, CEPI was working towards the development of vaccines against its priority pathogens. Whilst it continues to do this, CEPI is now supporting the progression of candidates right the way through to licensure as opposed to Phase II and investigational stockpile.
- Transform – This pillar focuses on advancing technologies and networks that will transform the response to future epidemic or pandemic situations. One of the main focuses is on virus family vaccine libraries.
- Connect – Conscious of the need for coordination across the ecosystem, CEPI strives to collaborate with other funders with similar interests, as well as to inspire other stakeholders to invest in pandemic preparedness.

All of this comes together and contributes to the '100 days mission' – to develop a safe and effective vaccine in 100 days from the moment that a pathogen is sequenced to initial availability for use.

Following over 50 interviews during which innovations from the COVID pandemic were reviewed, it became clear that compressing timelines of current approaches alone will not be enough to achieve the 100 days mission, and that there will need to be a paradigm shift towards maximising preparedness.

Areas of preparedness that need addressing can be broadly grouped into five categories: early warning, better biomarkers, prototype vaccines, trial infrastructure, and manufacturing. Although not all of these are for CEPI to address, there are a number that fall within the scope of CEPI 2.0, including the development of vaccine libraries:
The aim of CEPI's vaccine library programme is to develop an archive of prototype vaccines and immunogen designs for up to 25 viral families with the potential to cause future outbreaks. These activities will be critical for building knowledge and confidence in platforms.

Several technology-based approaches are already on CEPI's radar – including next generation mRNA, novel vaccine platforms, and manufacturing innovations such as platform optimization, synthetic biology approaches and rapid analytical testing – but CEPI welcomes contributions from the SAC on any other areas to investigate.
Some non-technology-based innovations in which CEPI is also planning to invest are: adjuvant libraries, clinical trial preparedness, manufacturing networks and sustainability, broadly protective coronavirus vaccines, regulatory preparedness, disease X libraries, and monoclonal antibodies – many of which the SAC would discuss in more detail over the following days.

Discussion

Alan Barrett suggested that 'education' should be added as a sixth focus area for improving pandemic preparedness. During the flu outbreak in 2009, it took three weeks to prepare for clinical trials as stakeholders were not sufficiently prepared to respond to the outbreak, with protocols either not ready or inadequate. In future, it will be important for all parties to be aware well in advance of what is required to deliver in 100 days.

Azra Ghani asked for clarification on what triggers initiation of the 100 days process, to which Richard Hatchett responded that day one is simply the day you decide to start. For COVID, CEPI's first investments were made on 23 January 2020, just 12 days after the sequence was made available.

Luciana Borio asked what happens if CEPI delivers in 100 days and makes 100m doses available, but the target populations feel it is too early and want more information before deploying the vaccine. Melanie advised that this is where collaboration with end-to-end partners becomes critical; CEPI's focus is on R&D and so in order to prevent such situations, downstream partners will need to be preparing in parallel.

Should CEPI invest in passive immunization?

Lastly, Michel De Wilde gave a presentation focused on the question, 'Should CEPI invest in passive immunization'.

Passive immunization is not a new concept, with over 100 approved monoclonals available today, including nine against infectious diseases. Some of the most critical in development include monoclonals against HIV, influenza, and RSV, with Nirsevimab (which induces a mutation in the mAb which allows an increase in the half-life sufficient to ensure protection throughout the RSV season) having been licensed for use in infants in just November 2022. However, even these most recent products have been developed in the 'traditional' way.

So, what's new?
There are three key areas transforming the monoclonal space: speed, scale and potency.

- Speed – There are several ways of isolating monoclonals. Currently, the fastest are: sequencing and functional selection. Both result in the collection of mAbs for further study which come from humans who have overcome infection. In one example, the time from receiving the sample to identifying the sequence was reduced to just 25 days.
- Scale – It is possible now to isolate >15k different mAbs from a single sample, which can allow for better identification of high potency antibodies.
- Potency – Studies on monoclonals against Rift Valley Fever conducted in 2021 achieved an IC50 value for neutralization of the indicated strain in the nanogram range. If we are able to extrapolate these protection data from mice to humans, the dose would be below 1mg, compared to the current range for monoclonals which is in grams.

All together, these advancements have the potential to drastically improve cost of goods, possibly even bringing monoclonals on par with some vaccines. As a reference point, using today's technology, mAbs cost approx. 100USD per gram. Other ways to reduce cost could be by using alternative production systems (e.g., fungi or milk of transgenic animals), gene-encoded delivery, or antibody-like molecules.

Beyond being a product themselves, monoclonals are also the basis of structural vaccinology, and so are critical for the development of successful vaccines. Prior to the COVID-19 outbreak, mAbs isolated from CMV convalescents were used to help identify the prefusion form of coronavirus spike proteins which led to the discovery of the pentameric-complex. A paper published in 2021 by Rino Rappuoli goes further in explaining this relationship.

There are of course limitations as well: extreme specificity is a challenge as, in the face of a rapidly mutating virus, the mAb may lose potency quickly. Of note, all SARS-CoV-2 mAbs have since lost EUL due to this effect.

For mAbs to be applicable in future pandemic situations, it will be important to find ways to anticipate viral evolution, or increase breadth through the development of multi-specific or multivalent antibodies.

For the best results, we will need to both reduce cost and increase breadth, and the best chance of doing so may be through the development and application of antibody-like molecules: nanobodies (produced in sharks and camels), and sherpabodies have both been shown to produce amazing results.

So, what should CEPI consider?
Michel's first recommendation was for CEPI to mirror its vaccine library efforts by generating mAbs against the same 25 viral families, noting that mAbs can be used not only to provide immediate protection but also to facilitate vaccine design. He advised using mAbs from convalescent individuals and focusing on maximising potency and breadth.

Secondly, he recommended that CEPI continues to stimulate innovation in the field by investing in novel approaches such as:

- Antibody-like molecules and multi-specific mAbs
- Biotherapeutics with broad antiviral efficacy
- Gene-delivered mAbs
- Alternative, lower cost manufacturing

Discussion

Linfa Wang strongly supported Michel's proposal, and in particular his recommendation for CEPI to start thinking of mAbs in the context of pandemic preparedness rather than therapeutics. He commented that having a broadly protective mAb ready to dampen the rate of infections and hold back the pandemic whilst vaccines are developed would be a very effective strategy and that mAbs and vaccines need to go hand in hand as described.

David Vaughn asked what the time for development of mAbs (from receiving human convalescent serum to a strain specific monoclonal being ready to go into Phase I) would be under ideal circumstances. Michel responded that he was not entirely sure, but noted that the 25 days mentioned does not include time to make the half life mutations and start production traditionally. All-in-all his assessment was 'not fast enough', but advised that it was something he felt could be improved. He would be interested to understand whether gene delivery (mRNA) might be a possibility for this.

Peter Smith agreed that price and cost are significant impediments to widespread use of mAbs, and that increases in potency will be critical to addressing this.

Manu Hanon highlighted that not all diseases will be able to be treated using this approach, and that antibody response is only one arm of an immune response.
However, he also added that a real positive aspect of mAbs is the fact that you can often predict quite precisely when the infection occurred, and so learn when an individual or population needs protecting and carefully time the administration in line with this (e.g., RSV at 2 months old).

Phil Krause was also supportive of Michel's recommendations, feeling that regardless of how quickly a vaccine is deployed, it will likely not be sufficient for preventing spread in a localised area given the delay that would be caused by waiting for the vaccine to induce a response. However, if there had been a COVID monoclonal (for example) available to use when the virus was still restricted to a single geographic area, it would have been able to take immediate effect and spread could be controlled more effectively. The difficulty we are facing now is that we are hoping to achieve both breadth and potency whereas there is usually a trade-off between the two. Phil suggested that, whilst early in a pandemic we may be able to do without breadth (and it may be difficult to achieve given the limited number of test cases available), for a monoclonal to be useful over time, breadth will need to be achieved.

Another issue that Phil highlighted was regulators' current perceptions of, and approaches to, monoclonals. His view was that, at present, regulators are unwilling to look at monoclonals against infectious diseases in the context of their mechanisms of action, and they insist on too much evidence, meaning that mAbs are unable to keep up with changing virus and maintain authorisation. If regulators were to accept neutralisation as a correlate of protection, manufacturers could quickly substitute in mAbs that bind to current strains. However, until such time, monoclonals are unlikely to be able to be deployed in this way. Luciana Borio agreed and said that it is a real tragedy (given mAbs may be the only option for some immunocompromised patients) that mAbs are not only not being authorised, but are losing authorisation as well, despite real-world data showing positive benefits.
Rebecca Grais added that there are not just regulatory barriers to the use of mAbs, but also practical barriers. The effectiveness of a mAb is limited by the biological conformation of a patient, and in the context of an epidemic or pandemic, this is often absent or delayed and so needs to be considered. In addition, if biological conformation is likely to be necessary for licensure, there needs to be an upscaling of that capacity otherwise the use case will be inherently limited especially in places where epidemics and pandemics are most likely to occur.

Lastly, Alan Barrett added that the critical path for making mAbs is twofold, given the need to not only identify which antigen to use (and ensuring the correct conformation), but also to decide what assay to put it in. He noted that SARS-CoV-2 monoclonals act very differently in different neutralisation assays depending on whether you use pseudovirus or real virus etc and that this is a challenge with monoclonals that could make developing a library of mAbs very difficult. Michel responded that this is why he favours mAbs from convalescents and would certainly recommend using them for the library approach.

ITEM 2: CEPI's manufacturing strategy (Plenary)

Led by: Anand Ekambaram

CEPI has recently established a dedicated manufacturing division, which exists primarily to support CEPI's 2.0 objectives by:

- Innovating in the vaccine manufacturing space – focusing on speed and manufacturability
- Providing CMC roadmaps for our products (a concept that is not new, but that is now more heavily informed the 100 days mission and equitable access)
- Establishing a geodiverse manufacturing network to address lessons learned from the pandemic
- Developing supply chain strategies to promote resilience
- Amplifying the impact of the work we do by working closely with policy-makers

Over the past six months, the team has been working to articulate a clear strategy for the division, and in order to do so, first worked to align on the most critical external challenges in the vaccine manufacturing space, as well as key internal priorities and needs:
External

- Inherent complexity of vaccines
- Lack of geodiversity
- Challenges of sustainability
- Fragmented R&D&M ecosystem

Internal

- CEPI 2.0
- Equitable access
- Disease portfolios
- Innovation support programmes
- Outbreak response

The strategy then aims to outline ways in which CEPI can add value in each space – our 'value proposition'.

It was acknowledged that the majority of the propositions featured in the manufacturing strategy speak to CEPI's 'prepare' and 'transform' pillars; however, the 'connect' pillar will also be highly critical for success.

As such, the manufacturing division will collaborate extensively with R&D, policy and resource mobilisation, finance, and pandemic preparedness and response in order to successfully deliver its divisional goals.

Discussion

The SAC was asked to consider the following questions:

1. Has MSC identified the most appropriate drivers in the context of CEPI's work?
2. MSC's value proposition – did we get this right?
3. Are MSC's core services aligned with CEPI's strategy and priorities?
4. Is there opportunity for MSC to deliver a 'quick win'?

Alan Barrett opened the discussion by asking whether there are opportunities to learn from other stakeholders' (e.g., Gavi, WHO) experiences of country vaccine implementation in order to guide selection of sites for the proposed manufacturing network. Anand Ekambaram responded that this should indeed play a role in informing site selection, and that it will be supported by our policy and resource mobilisation team's knowledge of country-specific conditions and challenges.

Stanley Plotkin then asked whether CEPI intends to establish new manufacturing sites, or invest in existing ones, cautioning strongly against the former as a strategy given the associated cost and time burden. He commented that there are a number of manufacturers that have emerged in recent years in developing countries that are doing work equal in quality to manufacturers in HICs. In response, Anand confirmed that CEPI's strategy is based on these principles i.e., seeking partners that already have core capabilities, and then driving maturation. Richard Hatchett and Manu Hanon echoed this point, agreeing that it should not be CEPI's responsibility to build new facilities, but rather to support growth and development of existing sites.

Regarding manufacturing lessons learned during COVID, Mahmudur Rahman commented that, in some cases, manufacturers were not able to meet the demand of the region because governments intervened and ring-fenced supply for country-specific use. In order to avoid this happening again, he advised that consultation with the governments of the countries in which the sites are located will be critical, and that agreements committing to regional and not only national supply need to be put in place. Anand again agreed, assuring the SAC that CEPI intends to address this issue in two ways; firstly, through dialogue with governments as advised, and secondly, through agreements with the sites that, if the product they are manufacturing becomes needed for pandemic use, manufacture will be proactively transferred to at least one other site for parallel production, to avoid becoming beholden to a single country's export controls.

Luciana Borio expressed real concern that the manufacturing network concept may be an example of something where policy has gotten ahead of practicalities; she commented that there is much enthusiasm around the idea, but not always due consideration or appreciation of the complexities - although there has been considerable conversation about building sites and human resource, she felt that there has been very little if anything to date about how to develop strategies for sharing consumables/assay development etc.

Luciana also spoke to Stanley's point, noting that time and money are not the only challenges associated with setting up new sites. Establishing sites that are dedicated to pandemic response only will not be sustainable, and so CEPI should look to partner with manufacturers that already have strong existing foundations that can be augmented in pandemic situations instead.
Richard Hatchett acknowledged and accepted the challenges associated with the explosion of innovation in this space, and advised that CEPI is therefore trying to be supportive but measured in its involvement.

In reference to Luciana's point about site sustainability, David Vaughn asked whether it might be feasible to use rapid response platforms to create updated EPI vaccines, and whether this could then work a strategy for maintaining sites during inter-pandemic periods. Melanie Saville responded that mRNA bacterial vaccines (for example) could well be possible; however, they may not be competitive with what is already out there with regard to cost/price or delivery, and so these challenges would need to be considered and resolved before it became a viable solution.

Phil Krause also responded to Luciana's points, agreeing that strong baseline capabilities will be an essential characteristic of any partner joining the network; however, he also felt that this may result in a trade-off whereby the geodiversity of the network is jeopardised, and so asked how CEPI would balance these two requirements. Anand advised that it will be essential to include some of these well-known high performing sites, as we will likely need to lean on them more in early stages as other sites mature; however, as time goes on, this reliance will reduce. To this point, Rebecca Grais strongly advised not to lean too heavily on western-focused manufacturers to lead preparedness of a Global South vaccine manufacturer as this could discourage engagement of others within the network from engaging within the same region. She suggested that placing partners like IPD (or CEPI) as intermediary in this role could be a good compromise but advised that engagement with others in the network would still need to be proactive and focus on demonstrating the value to them of the site selection.

Azra Ghani commended the holistic approach of the strategy but suggested that, when communicating to communities, CEPI could make even more of economic benefits of establishing local manufacturing capacity. She also raised the issue of sustainability related to staffing, noting that drafting in healthcare workers around outbreaks may result in pulling them away from already under-resourced primary care facilities. As such, it would be helpful to see CEPI's longer-term vision for managing this.

Lastly, Ken Ishii responded to CEPI's request for 'quick wins', suggesting that the most impactful thing to do could be to upskill staff at sites that are already well-versed in GMP compliance, training them in different biologics/platforms e.g. mRNA.
Alternatively, Phil Krause suggested a staff (and therefore knowledge) exchange, in which teams from developing sites would travel to well-established sites for training. Rebecca Grais was very supportive of this concept but suggested that the reverse approach would be more beneficial.

ITEM 3(a): Manufacturing technology roadmap (Breakout)

Led by: Ingrid Kromann, Ranna Eardley-Patel and Michel De Wilde

In vaccine and biologic development, there are two 'valleys of death'– the first stretching from the early research phase to human PoC data, and the second stretching from Phase III studies to commercialisation. CEPI 1.0 had a particular focus on supporting developers to bridge the first valley, but as we now move through the CEPI 2.0 period, CEPI is taking a much more end-to-end approach. The MSC division has developed a CMC framework (manufacturing technology roadmap) designed to help awardees move from development to commercialisation (bridge the second valley of death), as well as a series of other complementary tools which include: tech transfer guidance, a process development risk assessment template, an analytical maturity questionnaire, a COGs assessment, and a supply chain maturity questionnaire.

Discussion

The SAC was asked to consider the following questions:

1. What are the main technology roadmap implementation challenges, and which should we prioritise addressing in the next 2 years to best advance CEPI's existing portfolio?
2. What are the best strategies to bridge the R&D&M "Valleys of Death"? (e.g. for the Lassa programme)
3. How can CEPI's current manufacturing innovations program facilitate the paradigm shift to enable the 100 day mission?

What are the main technology roadmap implementation challenges, and which should we prioritise addressing in the next 2 years to best advance CEPI's existing portfolio?

Alan Barrett suggested that one of the biggest challenges to overcome may be awardees' baseline levels of expertise in areas within the technology roadmap. He advised that CEPI will need to educate, raise the level of expertise, and set appropriate expectations for manufacturing standards per platform.
Manu Hanon then asked to what extent manufacturability plays a role in investment decisions for R&D, suggesting that CEPI needs to consider the valley of death before selecting candidates, not only once awardees have been onboarded and are provided with the CMC framework.
The group also agreed that it is critical for CEPI to invest in people, ensuring appropriate expertise exists internally. Ingrid Kromann advised that CEPI has expanded to ensure coverage of both CMC and manufacturing domains, which the SAC acknowledged; however, they still advised that this expertise should be mirrored in a specialized network of external advisors in order for CEPI to be able to keep up with the pace of innovation and fully address each platform's challenges.

What are the best strategies to bridge the R&D&M "Valleys of Death"?

The discussion here focused mostly on CEPI's role as a matchmaker for developers and manufacturers. The SAC felt that CEPI could add real value by matchmaking and facilitating the formation of financially viable partnerships much earlier on, rather than at the point at which a developer reaches the second 'valley', and that the end goal should be that the two CEPI networks – of developers and of manufacturers - 'work as one'. However, the group also acknowledged that collaborations like this could be difficult to initiate without clear incentives for the IP holder, and as such, building business development expertise could also then become a critical part of the awardee education mentioned in question 1.

How can CEPI's current manufacturing innovations program facilitate the paradigm shift to enable the 100 day mission?

In reference to CEPI's 'speed' call for proposals that is shortly due to be launched, Luciana Borio suggested prioritising manufacturing innovations that aim to address already known barriers to the 100 days mission. She felt that this could help to narrow the scope of the programme which might otherwise be infinite. Manu Hanon agreed with this approach and in addition recommended engaging external experts who have first-hand experience of the challenges in question in the review of applications.

Ken Ishii commented that there is still a huge bias towards mRNA projects in the context of rapid response, but that there is a lack of coordination and information sharing in this space. As such, further investment into it may be a waste and he highlighted the importance of exploring/preparing a variety of platforms.
Manu agreed that variety is critical for the 100 days mission, but also urged CEPI to consider its R&D and manufacturing investments in the context of each other – i.e. if CEPI is already investing heavily in mRNA projects, it needs to make sure that this investment is mirrored in investments in manufacturing innovation so as to ensure fully considered, end-to-end process can be deployed in an emergency situation.

Lastly, Paula Bryant commented that, in 2006 DARPA launched its Accelerated Manufacturing of Pharmaceuticals (AMP) programme. This was also dedicated to increasing speed in manufacturing, but focused on protein-based vaccines and monoclonals. This subsequently evolved into many different programmes, and they have just launched the 'Now' programme focusing on nucleic acid vaccines. The key point was that efforts to increase the speed of vaccine manufacture have been going for a very long time and it is not just a CEPI problem – it is something that requires broad collaboration. She advised CEPI to leverage previous efforts and not reinvent the wheel.

ITEM 3(b): Manufacturing network and sustainability (Breakout)

Led by: Matthew Downham, Diletta Magini and Dominique Maugeais

As discussed during the earlier plenary session, CEPI is looking to geodiversify vaccine manufacturing in order to ensure that in the future, production capacity exists closer to where emerging infectious diseases and outbreaks may occur (with a focus on LMICs). CEPI's target is to have at least five partners confirmed

across two LMIC regions by the end of 2026, with the target profile being human vaccine manufacturers that are already functional, self-sustaining, and commercial entities.

Following an expression of interest issued in 2022, CEPI received over 70 responses from vaccine manufacturers, which were subsequently scored against a set of seven core criteria, and a shortlist of nine potential partners created. Two contracts have already been signed (IPD, Senegal and Aspen, South Africa). For each site on the shortlist, CEPI has identified critical gaps in platform technology capabilities, and potential disease targets from the CEPI portfolio on which to collaborate. Of note, CEPI acknowledged the importance of working with the WHO on this project given the potential crossover with their mRNA network programme.

Following the introductory presentation, Kent Kester queried how CEPI can ensure that any investments made in building sites' mRNA capacity will be adequately leveraged, given CEPI cannot be involved in decisions regarding how to maintain this function during inter-pandemic times. Matthew Downham advised that many of the sites being considered are already very actively considering this question for themselves, and that ultimately the decisions will be made in collaboration with the associated governments.

Secondly, Kent noted that CEPI has hopes that its efforts in geodiversification will lead to greater equitable access; however, EA is firmly a policy rather than operational issue, and so could be perceived as out of scope. Matthew acknowledged this point, agreeing that policy discussions should likely not be a part of the manufacturing network efforts, but argued that simply by positioning a facility within an LMIC, you are facilitating equitable access by default.

Luc Debruyne commented that access only really becomes an issue - and therefore local manufacturing a priority – during pandemic (as opposed to epidemic) situations, when governments may ring-fence doses for national or regional supply. A number in the group therefore suggested that it may be sensible to continue manufacturing epidemic vaccines in countries and facilities with greater regulatory and personnel capabilities, as this could feasibly result in LMICs gaining faster access to vaccines than they might do if doses were to be manufactured in their own or other countries where regulatory processes may be slower.

In contrast, Phil Krause made the point that LMIC facilities will only be sustainable and able to respond to pandemic demand if they are already 'functional, self-sustaining, and commercial entities' during inter-pandemic times. As such, he suggested that governments and international procurement bodies may need to consider proactively buying doses of epidemic vaccine manufactured in these facilities (despite potentially non-competitive pricing or slower regulatory procedures) to 'keep them warm' for pandemic response. Many of the group felt that this approach has too great a trade-off, as it could cause production and access to be significantly delayed, and so instead proposed that CEPI investigates tech transfer agreements with its HIC facilities, to enable LMIC facilities to quickly build capacity in the event of a pandemic.

Regardless of the selected approach, it is still possible that governments may be unwilling and/or unable to pay for non-competitively priced doses (either epidemic or pandemic), and this was ultimately acknowledged as the elephant in the room – that if there is not a sustainable dose procurement system/agreement in place thereby securing the 'business' for LMIC facilities, there is little value establishing the network.

Discussion

The SAC was asked to consider the following questions:

1. How should CEPI help overcome MfG-Supply Chain sustainability challenges for Vx manufacturers in the global south?
2. What should be our highest operational priorities for Vx MfG geo-diversification e.g., to meet workforce training needs?
3. In Dec'26 what will success look like for CEPI's Vx MfG preferred partner facility network?

How should CEPI help overcome MfG-Supply Chain sustainability challenges for Vx manufacturers in the global south?

- As mentioned above, sustainability of facilities in LMICs was seen to be dependent on enablers such as Gavi, UNICEF, PAHO and governments committing to procuring doses from them. It was acknowledged that CEPI cannot be a decision-maker in this context but can still play a critical enabling or facilitating role.

What should be our highest operational priorities for Vx MfG geo-diversification e.g., to meet workforce training needs?

Although acknowledging that some risk may need to be accepted, the SAC recommended that CEPI only works to establish vaccine manufacturing capacity and capability in sites for which they are confident a sustainable procurement agreement can be reached (i.e., is already in discussion).

In Dec'26 what will success look like for CEPI's Vx MfG preferred partner facility network?

The SAC felt that the definition of success would be different for each partner site, dependent on their current level of capability. For sites that are classified as 'advanced', success would be outcome-based e.g., readiness to launch a vaccine for a CEPI priority pathogen, whereas for 'expert' or 'competent' sites, success would be demonstrated by process or capacity improvements e.g., establishment of CTM supply on a new platform.

ITEM 3(c): Clinical research preparedness (Breakout)

Led by: Christof Vinnemeier and David Vaughn

CEPI recognises that achievement of the 100 days mission will be dependent on sustained, global, clinical research preparedness, and as such is looking to support international networks of clinical trial sites which will be primed to respond in the event of an outbreak. However, for this approach to be sustainable, it will be critical to ensure that partner sites are not only able to respond rapidly, but are also routinely conducting clinical research to maintain staff and expertise in 'peacetime'.

Following extensive stakeholder engagement, CEPI has therefore drafted a strategy for research preparedness that is based around two tracks:

- Track A – 'peacetime' – facilities are in a state of routine research, including advancing CEPI's core vaccine portfolio
- Track B – 'outbreak' – facilities are in a state of 'clinical evidence generation readiness'

CEPI will be taking a multi-regional approach to this strategy, but will be starting with West Africa as a Pilot region based on the urgent need to prepare for a Lassa Phase III efficacy trial, and the end goal of the upcoming call for proposal will be a consortium led by a 'technical coordinating partner'.

There will be no need for national health authorities to respond to this call as they will be automatic and essential partners in this strategy, and it was emphasized that the primary work packages for both tracks will begin with very extensive stakeholder engagement.

Of note, four key principles will guide the implementation of this strategy, following the establishment of the consortium:

- Sustain investments – evolve from routine clinical trials to long-term investments
- Maximise synergies – explore commonalities and opportunities for co-funding with other funders and facilitators in the ecosystem, and leverage/learn from similar programmes
    - This point was repeatedly highlighted by the SAC members throughout the discussion.
- Align with national priorities – support existing local epidemic preparedness and endemic disease research programmes
- Promote local guidance – drive local ownership of the processes (seen as a prerequisite for achieving sustainability)
    - On this point, Alash'le Abimiku commented that, in the last few years, the NIH has been giving extensive research grants to programmes led by African Scientists, and in parallel established steering groups of the associated policy makers and governments. She advised that the frequent engagement of these policy steering committees was instrumental in driving country ownership and so could be a very effective strategy to employ in this programme as well.

For clarity, Alash'le also asked whether the tracks are mutually exclusive, or whether there might be a situation where a set of clinical trials focusing on endemic disease are expanded to collect data for an outbreak situation, and Christian Vinnemeier confirmed that the plan is exactly the latter. Peter Smith later commented on this, saying it is perhaps not wise to play 'Russian roulette' and hope that an outbreak

happens near one of your clinical trial sites, but instead plan to mobilise experienced staff from these sites to support a localised outbreak response elsewhere.

A number of SAC members suggested re-considering the name of the 'technical coordinating partner' (TCP), and instead using 'secretariat' or similar, given the role will be more one of coordination than direction, and also advised that the call should strive to avoid appointing 'the usual suspects', to support better geographic diversity.

Finally, Josie Golding also asked if there is a working example of Track B that could be shared, to which Christof Vinnemeier responded that CEPI had considered drafting this for the CfP, but took the decision not to include it as the scope and path for Track B really needs to be driven by country partners, and so will be shaped subsequently.

Discussion

The SAC was asked to consider the following questions:

1. Does the SAC feel there are any other things to consider for preparation of clinical trial sites in West Africa for the Lassa phase III vaccine efficacy trial?
2. The replication of this approach in other regions, for other pathogens or outbreaks, will form the basis of our longer-term approach to emergency evidence generation readiness. What are the SAC's considerations in terms of making this approach sustainable?
3. Where do you see a role for a global service provider in CEPI's approach to research preparedness?

Does the SAC feel there are any other things to consider for preparation of clinical trial sites in West Africa for the Lassa phase III vaccine efficacy trial?

Stanley Plotkin and Peter Smith emphasized the importance of clear communication both ahead of and during a clinical trial. They noted that it is critical for gaining initial trust in the community, but also for maintaining engagement throughout the study, particularly with a disease such as Lassa, which for many presents mildly or asymptomatically, which in turn could lead to limited uptake and follow-up attendance. Christof Vinnemeier strongly agreed with this, advising that CEPI intends to follow the example provided by the Lassa ENABLE programme and develop tailored and comprehensive stakeholder engagement roadmaps per country.

Regarding study design, Stanley suggested that any control studies be set up in a 2:1 ratio, as this can really support community acceptance.

Mahmudur Rahman also suggested that ethical and regulatory capabilities should be a key consideration for selecting the country in which the study will be held.

Rebecca Grais added that it will be critical to include WHO and authorities in West Africa in reviewing the compilation of the sites.

The replication of this approach in other regions, for other pathogens or outbreaks, will form the basis of our longer-term approach to emergency evidence generation readiness. What are the SAC's considerations in terms of making this approach sustainable?

A number of SAC members advised that partner sites in the programme would need broad capabilities (surveillance, diagnostics etc) and/or multiple research tracks, i.e., multiple income streams in order to be sustainable longer-term. For those who may not have such broad capabilities, enabling and encouraging collaborative use of resources across the network (e.g., ability to send samples for diagnostics elsewhere) will be vital. As CEPI cannot be everywhere at once to support this kind of collaboration and coordination, the SAC felt that it would be critical to establish regional support centres supported by multiple funders.

Further ideas on ensuring sustainability included identifying partners for global coordination of activities such as the advancement of in-country rapid regulatory review systems, supporting database harmonization across the network, and establishing protocol libraries with as many pre-approved protocols as possible.

The group lastly raised concerns about how to sustainably divert staff towards emergency response efforts without impacting the provision of core health services in under resourced areas. Although initially discussed in relation to the Lassa trial, it was acknowledged that this point would be relevant for all activities related to the research preparedness strategy.

Where do you see a role for a global service provider in CEPI's approach to research preparedness?

David Vaughn opened the discussion by suggesting that a global service provider could support regional centres through GCP training, contribute to finding research studies for the network sites, provide surge capacity for large outbreak response, and/or provide rapid response teams.

Rebecca Grais agreed strongly with the point regarding training but felt that GCP training alone would not be at all sufficient. Her view was that all aspects of management (e.g., financial/HR practices) should be considered.

Day 2

ITEM 1: Pandemic influenza (Plenary)

Led by: Melanie Saville and Anand Ekambaram

Over the past six years, CEPI has often considered how or whether it should be involved in influenza vaccine development. In general, the board has taken the view that flu already has a well-financed ecosystem, and so it should not be a priority for CEPI.

However, it is also acknowledged that flu projects could be used to support the advancement of new platforms, in particular, mRNA technologies, and more recently, the high frequency of outbreaks (e.g. H5) has triggered the board to ask CEPI what it would do in the specific context of pandemic flu.

As such, CEPI has recently begun work to outline the different roles it could play in the event of a novel flu outbreak today, in six months, or in two years' time, based on the ever-changing landscape.

ITEM 2: Evolving the BPCV portfolio (Plenary)

Led by: Nadia Cohen

In 2021, the focus of the CEPI BPCV programme was on SARS-CoV-2 variants of concern and Pan-Betacoronavirus vaccines. However, since then, variants have evolved, bivalent vaccines have become available, and the clinical and regulatory landscape has evolved, as has our scientific understanding (e.g., re humoral immunity and the key role of T cells in breadth of protection and prevention of severe disease). As such, CEPI is now considering how it needs to reshape its portfolio to fit with changing global priorities and activities.

Based on the above, CEPI's current plan is to

a) focus on developing a broadly protective Pan-Sarbecovirus vaccine with a near-term path to licensure, and
b) develop strategies against future threats in the coronavirus family, with no near-term licensure goal

For context, Nadia Cohen then gave a brief overview of the current CEPI portfolio as well as the success criteria that will be used to assess potential pan-Sarbecovirus candidates:
For pre-clinical proof of concept:

- Statistically significant neutralising antibodies against circulating strains, past variants of concerns and other sarbecoviruses known to infect humans (e.g., SARS-1)
- T cell responses to the same groups of viruses
- In vivo protection against circulating strains and SARS-1 that is equal to or better than a licensed comparator.

For clinical proof of concept:

- Neutralising antibody response to circulating strains that is equal to or greater than that which is offered by existing vaccines.

With regards to the proposed success criteria, Azra Ghani suggested that the use of neutralising antibodies for pre-clinical proof of concept of new candidates needs more thought as a) clinically significant differences in neutralising antibodies may not directly translate into clinically significant differences in clinical protection, and b) a new candidate that does not demonstrate non-inferiority against current variants could end up being very effective against a new variant in the future, and so you risk throwing out something of great value.
In response to Azra's second point, Linfa suggested that CEPI tests pre-clinical candidates against potential future circulating variants (those currently in pangolins and bats) as well as current human variants in order to gain a view of the totality of data available before making down-selection decisions.

Discussion

The SAC was asked to consider the following questions:

1. What is/are the use case(s) for broadly protective coronavirus vaccines, and what TPP(s) - primary product indication, target population, efficacy, durability, regimen etc. - should we be working towards?
2. What does emerging science suggest in terms of the achievability of broad protection in the Coronavirus family?
3. What are the most promising technical approaches to achieving broad protection?
4. Would a coronavirus-specific vaccine library (as is being developed for other virus families in the Disease X program) represent a useful alternative to a Pan-corona vaccine and have the potential to meaningfully accelerate vaccine development in the event of the emergence of a novel coronavirus disease of pandemic potential?

What is/are the use case(s) for broadly protective coronavirus vaccines, and what TPP(s) should we be working towards?

Linfa Wang suggested that a clear use case for a Pan-Sarbecovirus vaccine would be as a heterogenous booster in the general population. However, he raised concerns that it may be difficult to obtain licensure for a vaccine against a virus that has not yet crossed over into humans. For example, a developer may have a vaccine showing statistically significant neutralising antibodies against pangolin or bat virus, but regulators may not be willing to accept in vitro data only as sufficient to give the go ahead for a Phase 1 human trial.
Phil Krause acknowledged the difficulties that developers sometimes face in progressing to Phase I in these situations, but also commented that regulators are not in the market to prevent broadly protective vaccines. His suggestion was to first pursue a coronavirus indication, declaring intent to collect additional data on broad protection once licensed.
Phil also cautioned against describing these hurdles to licensure as 'regulatory' hurdles and instead encouraged the room to recognise these as 'scientific hurdles', or in fact just reduced demand; he and Melanie agreed that as most people now have some natural immunity against COVID, a vaccine will need to demonstrate either protection against severe disease, or greater durability in order to be an attractive proposition. Adam Hacker responded that, from a regulatory perspective, there is no agreed marker for severe disease and so this will be incredibly difficult to license for; however, Phil Krause felt that demonstrating both cellular and humoral responses could help put a developer's case that the vaccine might be more effective in preventing severe disease in the future.

Christian Drosten took a different view, and asked whether we really believe that a new ACE-II binding Sarbecovirus will emerge given the ongoing circulation of, and vaccination against, SARS-CoV-2 variants. He suggested that MERS represents a much more relevant and ongoing threat that CEPI could prioritise instead. He also highlighted that, before the pandemic, there were four established human respiratory coronaviruses circulating – two alpha and two beta – and so questioned the rationale of focusing only on betacoronaviruses given there are a number of livestock-associated alpha coronaviruses which could still pose a threat.
In response, Linfa commented that, even if we do not see a new Sarbecovirus emerge, the current SARS-CoV-2 vaccines will not protect against spread in the event of a SARS-1 outbreak, although they could support with protection against severe disease. Christian felt that this was sufficient reason to deprioritise Pan-Sarbecovirus vaccines, but Richard Hatchett commented that, if a more transmissible SARS-1 related virus were to emerge, even if saw a reduction in lethality of ~90% in line with COVID as a result of current vaccines, this would still leave us with a virus with a catastrophic 1% lethality. Christian acknowledged this, but responded that the virus has been highly conserved to date, and so he wouldn't expect dramatic mutations affecting transmissibility now.
In response to Christian's comments around MERS, Chris Da Costa added that some of the candidates within the portfolio include a MERS antigen as part of their broadly protective approach, and we do still have a standalone MERS portfolio.

What are the most promising technical approaches to achieving broad protection?

Stanley Plotkin commented that prospects look good regarding the scientific feasibility of broad protection and in particular the data related to CD8 T cells and cross reactivity. His recommendation was that CEPI should support work on this, which Alash'le Abimiku agreed with, feeling that CEPI has a brilliant opportunity to review what we have learnt about T cell responses and protection, innate immunity, and in particular why the impact of SARS-CoV-2 in Africa has not been as expected. She noted that in the last 10 years, the NIH has spent significant funds to establish three biorepositories capable of storing viable T cells which would enable clinical networks in developing countries to test some of these assays.

Alan Barrett provided a different perspective, commenting that there is so much happening in the coronavirus space (>900k publications to date) that we can't possibly be aware of all of the technologies in development. As such, rather than isolating a particular technology to focus on, he suggested that CEPI considers an annual rotation of seed funding, seeking innovations related to adjuvants, platforms, and antibodies etc.

ITEM 3(a): CfPs in development – Adjuvants (Breakout)

Led by: Daniel Fullen and Ken Ishii

The adjuvant landscape is a complex space, currently driven by a small number of global health partners; BMGF, NIH, Right and CEPI. These partners are working together to ensure synergies and avoid overlap, and have identified the following critical challenges for adjuvants in the context of pandemic preparedness:

- De-risking – as adjuvants cannot be licensed in isolation, we are reliant on data from vaccine developers who are using them in clinical trials.
- Access – due to restrictions put in place by IP holders, developers often select adjuvants for trials based on what is available rather than what might be the best pairing for their vaccine candidate, which has the effect of further reducing the data pool.

As such, CEPI has developed the following objectives for its work in this field:

- Establish an adjuvant library initially focused on licenced and other emulsion and Liposomal based adjuvants
- Establish a screening process that enables vaccine developers to select the most appropriate adjuvant for their needs
- De-risk adjuvants by advancing development of adjuvanted vaccines toward licensure
- Broaden access to de-risked adjuvants
- Develop a database to identify optimal adjuvants for particular antigens and platforms

In its upcoming call for proposals, CEPI will begin by requesting preclinical and clinical data for different adjuvants, so that it can review and make an informed decision as to which adjuvants should be included in the library. Physical samples will then be stored at the NIBSC, and CEPI will work to support its partner developers to select the best adjuvant for their specific antigen by running head-to-head preclinical studies within the CEPI animal network, comparing multiple adjuvants using a standardised protocol. The condition of this support will be non-exclusive access to the adjuvant the developer ultimately selects, so that other developers can still use it in future.

Discussion

The SAC was asked to consider the following questions:

1. What should be the selection criteria for adjuvants for an expanded adjuvant "library"? (Selected adjuvants to be evaluated with vaccine candidates in preclinical studies in order to increase the chances of the right adjuvant being selected for the right vaccine)
2. How can lead adjuvants from preclinical studies be further de-risked, and should CEPI fund the development/production of particular adjuvants at risk?

3. What can CEPI do to improve global access and supply of adjuvants (e.g., promote GMP production of lead adjuvants in different regions)?
4. How can/should localised production of sustainable raw materials (e.g., squalene, QS-21, etc.) for adjuvants be increased with a view to de-risking supply chains?

What should be the selection criteria for adjuvants for an expanded adjuvant "library"?

Mike King expressed some concern about CEPI's proposal, suggesting that it is trying to screen and reidentify adjuvants of interest, something that could be very time consuming but ultimately return the same information we already have; that liposomal and emulsion-based adjuvants can be effectively produced at scale, but that only emulsion-based adjuvants are likely to be compatible with a pandemic environment. As such, he advised CEPI not to restart the process of screening de novo, and instead to prioritise adjuvants for the library that we already know can be manufactured at scale and speed in pandemic situations, and which are likely to be compatible with more than one type of antigen. Michel De Wilde strongly agreed with this, and added that he understands there to be no further IP issues with emulsion-based adjuvants following the COVID-19 pandemic. As such, he felt that a strong starting point for CEPI would be to prioritise making these raw materials available.

Nathalie Garcon advised that, given the high number of variables that will affect optimal adjuvant choice, it is important that the library be diverse, and feature adjuvants with a variety of mechanisms of action and activity against TLRs.

How can lead adjuvants from preclinical studies be further de-risked, and should CEPI fund the development/production of particular adjuvants at risk?

Krishna Mohan suggested that, before prioritising any adjuvants for further development, extensive WHO/FDA toxicity studies should be done. He acknowledged that this can be time consuming and so suggested it would be worth investing in toxicity packages pre-emptively so that access to adjuvants would not be delayed in a pandemic situation.

Daniel asked if there are specific adjuvants that CEPI should prioritise for investment in toxicity studies or GMP manufacturing, to which Krishna responded that a selection of a small number of adjuvants should be made based on preliminary literature research. Nathalie Garcon added that it would be important to know the mechanism of action of any adjuvants being tested as this will give an indication of where you might expect to see reactogenicity signals.

What can CEPI do to improve global access and supply of adjuvants?

Ken Ishii suggested that there is a greater access issue related to adjuvants for use in Phase I trials than for preclinical trials, and as such suggested that CEPI instead considers providing GMP lots with multiple adjuvant choices.

Ken also suggested that supporting the certification of mimics will play a crucial role in alleviating access challenges. However, Nathalie Garcon raised concerns that the use of mimics may be a much longer-term strategy, saying that she is yet to see any studies that demonstrate that mimics can have an effect that is comparable to the adjuvants they imitate.

How can/should localised production of sustainable raw materials for adjuvants be increased with a view to de-risking supply chains?

In general, the group agreed that global access to adjuvants needs to be improved, but that this should not necessarily be achieved through local manufacturing. Instead, the group felt it would be more sensible to establish in-country adjuvant stockpiles to alleviate the impact of borders closing during pandemic

situations. However, it was equally acknowledged that there are outstanding challenges related to storage method (vial vs lyophilized bulk).

It was also agreed that there is a need to look at increasing the diversity and supply of different adjuvants to ensure that there is not a dependency on just a few adjuvant providers.

ITEM 3(b): CfPs in development – Broadly protective filovirus vaccines (Breakout)

Led by: Gerald Voss and Phil Krause

It is often acknowledged that CEPI was 'born' out of the Ebola crisis of 2014-2016, and so although it is not one of the priority pathogens, in 2018, the board tasked CEPI with 'finishing the job', i.e., supporting a number of late-stage clinical trials to enable the licensure of a second Ebola Zaire vaccine. This has since been achieved, but we are now in a situation where we are seeing repeated filovirus outbreaks (e.g. Marburg in Ghana and Tanzania, and Ebola Sudan in Uganda) and so CEPI is reconsidering its role in this space. At present, CEPI's suggested approach is to support the development of a broadly protective filovirus vaccine for prophylactic use, in the hope that the value-add of broad protection could help to combat some of the Ebola Zaire vaccine implementation challenges currently seen in East Africa.

Discussion

The SAC was asked to consider the following questions:

1. How would you rate the scientific feasibility of developing a broadly protective Filovirus vaccine?
2. Which technical approaches do you feel are most promising?
3. What would be the regulatory path to licensure?
4. What would be potential indications for such a vaccine?

How would you rate the scientific feasibility of developing a broadly protective Filovirus vaccine?

The group agreed that it would be scientifically possible to develop a broadly protective filovirus vaccine. However, there may be some risk of immune interference and immune-dominance, which has not been widely investigated in animal models to date.

Which technical approaches do you feel are most promising?

The SAC was unanimous in favouring a multivalent approach, feeling that it may not be possible (in the near-term, and without significant technological innovation) to create a single immunogen against Ebola Zaire, Marburg and Ebola Sudan given their disparate phylogenetic lineages.

What would be the regulatory path to licensure?

Adam Hacker agreed with earlier comments that obtaining human efficacy data via ring vaccination studies would be challenging, and as such questioned whether there are sufficient similarities in the aetiology and epidemiology of Marburg/Ebola Sudan and Ebola Zaire to carry across data via immune-bridging if using the same platform (as was done with COVID strain changes). He also suggested that if the multivalent filovirus vaccine were to contain a component from an already-licensed monovalent Ebola Zaire vaccine, it may be possible to argue that the new formulation would maintain the monovalent vaccine's positive risk-benefit profile.

Although this approach would still likely only lead to an Ebola Zaire indication, it could accelerate deployment and allow for real-world evidence generation leading to a subsequent re-labelling.

ITEM 4(a): CfPs in development – Innovations in biologics (Breakout)

Led by: Stacey Wooden and Alan Barrett

In December 2020, CEPI took the decision to expand its scope to include support for the development of 'other biologic countermeasures', in addition to vaccines. This specifically refers to work on monoclonal antibodies and antibody-based biotherapeutics.

Based on some of the known limitations of monoclonals as therapy, CEPI decided to focus on the use of monoclonals as pre-exposure prophylaxis for outbreak pathogens (Nipah, coronaviruses and filoviruses) – as opposed to endemic pathogens (Lassa, Rift Valley Fever, Chikungunya) – with the idea being that administration at the start of an outbreak would help to reduce the amount of circulating virus, preventing an epidemic, and bridging the gap between the onset of the outbreak and availability of a vaccine.

In addition, extensive engagement with global funders, developers and researchers highlighted that, while the early discovery and pre-clinical development space for monoclonals is very crowded, there is currently significantly less support for the later stages of development; in particular, Phase II/III, licensure and stockpiling. As such, this is a niche that CEPI is looking to occupy; an approach which the SAC was unanimously in support of.

In line with the above, CEPI therefore set a target for CEPI 2.0 to have one Nipah monoclonal antibody ready for reactive use during an outbreak, and to stockpile 10k doses in Southeast Asia.

CEPI is also proposing to launch an 'Innovations in biologics' call for proposals, in an attempt to address three key challenges that were encountered in the development of COVID-19 mAbs:

- High cost of goods
- Risk of viral escape
- High concentration of IV administration required in early disease

Out of scope will be:

- Manufacturing or cell platform innovations solely
- Delivery devices for mAbs or biotherapeutic modalities (due to additional device QC required, increased likelihood of bacterial infection, and increased plastic use)

CEPI is looking to grant 10-12 smaller awards, in order to push late stage pre-clinical/pre-IND candidates through the pipeline and quickly identify what's working vs what's not.

Discussion

The SAC was asked to consider the following questions:

1. What are the priorities that should be addressed in the Innovations in Biologics CfP?
2. Are there other innovations or strategies that you believe CEPI should consider at this time?
3. How can CEPI leverage the success of mAbs for oncology to mAbs and antibody-like molecules for pandemic viruses?
4. What challenges do you foresee by adopting a portfolio approach with the Innovations in Biologics CfP?

What are the priorities that should be addressed in the Innovations in Biologics CfP?

The SAC agreed that the focus of this CfP should be to develop and stockpile a 'cocktail' of broad neutralising antibodies for prophylactic use against filo- or coronaviruses. They commented that this approach could be more effective than a broadly protective vaccine, as mAbs would not be reliant on immunogenicity in the same way that a vaccine would, and could therefore be tested in advance, further reducing the time between an outbreak and the availability of a biological countermeasure.

The SAC was also in support of CEPI investing in projects looking at how to leverage mRNA technology for fast, large-scale production of monoclonals or antibody-like molecules (such as nanobodies) in the event of an outbreak, in preference to continuing to use suboptimal cell bank approaches. However, it was clarified that CEPI will not be looking for projects that are solely focused on manufacturing innovations, and such research would need to be tied to a product.

The SAC also recommend exploring IM administration and non-device aerosols, given the target pathogens are predominantly respiratory and intranasal administration could contribute to higher potency, which would in turn be critical for achieving lower COGs.

Are there other innovations or strategies that you believe CEPI should consider at this time?

The SAC was unanimous in its support for monoclonals as the priority biological countermeasure for CEPI to pursue, agreeing that small molecule antivirals do not fall within CEPI's remit.

What challenges do you foresee by adopting a portfolio approach with the Innovations in Biologics CfP?

Products for the pathogens that CEPI works on may be perceived as having 'easier' paths to licensure due to their 'crisis' status and associated high mortality. As such, developers may be more likely to take risks with innovation, which could translate into a higher rate of failure in CEPI's investments.

In addition, the majority of mAbs developers are currently in oncology, and so CEPI needs to consider ways to incentivize them into the infectious disease space. One possible approach that CEPI is considering is to allow developers to generate proof of concept for the technology through work on an oncology indication, but on the understanding that they also develop the technology for one of CEPI's pathogens in parallel.

The SAC responded to this idea suggesting that applicants coming to CEPI who have been unable to secure funding for oncology may not be the strongest candidates, and so instead, CEPI should make funding conditional on the developer having already secured support for their oncology indication.

ITEM 4(b): CfPs in development – Controlled Human Infection Models (CHIM) for Beta-Coronaviruses (Breakout)

Led by: Christine Dahlke and Stanley Plotkin

CHIM is one of the more controversial subjects in vaccinology; however, when following modern protocols, it can be done in a very ethical and safe way and be a very useful tool. As such, the field is expanding, with organisations such as 'One day sooner' being established to recruit participants, and institutions such as the NIH, Oxford University and Imperial College London starting to conduct human challenge studies, with others following suit.

Some of the main applications of CHIM are: determining infectious doses of viruses, understanding pathogenicity and human-virus interaction, investigating whether a vaccine against one agent is protective against another, and importantly, studying mucosal immune responses: Despite the knowledge that SARS-CoV-2 is largely a mucosal infection, very few even experimental vaccines have been developed based on mucosal administration, demonstrating how little we currently know about how to induce mucosal responses.

In 2022, a workshop between CEPI, NIAID, Wellcome, BMGF and BARDA aimed to define the basic, translational and clinical research gaps impacting mucosal vaccine development for SARS-CoV-2, and the main conclusions were that:

- The best route of administration and vaccine platform is unclear
- Animal models are not predictive of human response
- Clinical trials to assess viral transmission are challenging
- There is a need for mucosal correlates of protection and standardized sampling methods

In addition, it was acknowledged that although current licensed SARS-CoV-2 vaccines are highly protective against severe disease, they are often not very effective at preventing infection or transmission which can pose a problem for high-risk populations, and further to that, viral spread and consequently emergence of new variants would continue. As such, CEPI plans to develop a beta-coronavirus CHIM and use it as a tool to investigate mainly two areas: How to flatten epidemic curves (reduce transmission and infection), and how to induce mucosal immunity. SARS-CoV-2 human infection models have previously been conducted by Imperial College London and Oxford University using the pre-Alpha Wuhan strain in naïve and non-naïve adults. CEPI will be focusing on beta-coronaviruses including SARS-CoV-2 variants of concern and seasonal beta-coronaviruses.

CEPI's proposal is to develop a consortium to enable the harmonized running of CHIM studies starting from virus isolation through to CHIM-based vaccine trials and beyond. The programme will be co-funded by HERA, and the proposed work packages have been approved by the EC, with signature expected within 3 months (end of July 2023).

Discussion

The SAC was asked to consider the following questions:

1. How would a CHIM programme/consortia be constituted in order to fill important gaps in the field of mucosal immunity and the evaluation of transmission-blocking vaccines?
2. How do you see the role of CHIM as an R&D methodology in the field of beta-CoV vaccines to provide important data on vaccine efficacy and vaccine-induced mucosal immunity & transmission-blocking potential?
3. What criteria would you use to select promising mucosal vaccine candidates for CHIM-based vaccine trials to assess transmission blocking? (e.g., platform, route, device, clinical development stage, etc.).
4. Which experimental approaches and which parameters would you focus on and use to assess and harmonise mucosal immunity and transmission?

David Vaughn asked whether the budget shared will cover vaccine evaluation or only development of the model, and Christine confirmed that it would cover both. David also asked whether applicants to CEPI's call will propose specific vaccines as part of their application or whether this will this be decided later.
Christine responded that the process of vaccine selection will be part of a work package. The awardees will need to develop an unbiased process to select vaccine candidates tested using CHIM. Support by CEPI and/or WHO to develop the process will be considered.
Ken Ishii recommended implementing animal models to evaluate a potential surrogate for prevention of infection and/or transmission. Mucosal tracing can be evaluated and compared to humans. Christine responded that CEPI's Animal Network will be involved.

How would a CHIM programme/consortia be constituted?

Josie Golding began the discussion by asking whether there would be room for less mature sites in the consortium or if only well-established institutions would be selected. Alash'le Abimiku added to this, asking if there are any established sites in LMICs.
Christine Dahlke responded that CEPI and HERA are not looking to build capacity in newer facilities, but that there is interest in engaging new investigators. Stanley Plotkin supported this approach, stating that the use of first-rate facilities will be absolutely critical.

How do you see the role of CHIM in the field of beta-CoV vaccines?

In general, the group felt CHIM to be a relevant and effective model; the group pointed out that Serum IgG or IgA alone are not solely predictive of protection, and neither is the T cell response. Therefore, as CHIM generates a set of multiple samples from different timepoints and different origins (air from breath, saliva, nose, PBMC, serum) it represents a good model for mucosal immunity studies.

However, Phil Krause expressed concerns about whether it would be feasible to accurately assess transmission blocking in the context of beta-coronaviruses. Given the high level of background immunity that would likely be found in participants due to previous SARS-CoV-2 vaccination and/or infection, investigators may be forced to use artificially high infection doses in order to achieve sufficient infection rates in the cohort and subsequently identify statistically significant differences in transmission rates. To combat this, the group agreed that there is a need to define a population in which an evolution of mucosal response can be evidenced. The ideal scenario would be to recruit entirely naïve subjects, but this was seen as unlikely to be feasible and so the group instead recommended that CEPI looks to recruit participants with low antibody titres (indicating that they were vaccinated a long time ago or had a low initial response). Regardless of the surrogate marker selected, it was emphasized that the level of background immunity across participants would need to be standardised. Manu Hanon expanded on this, encouraging CEPI to not only

assess and standardise initial antibody response but also cell mediated response, something he does not believe has been done before in challenge models. Christine agreed with this aspect and confirmed that cellular immunity will be part of the programme.

Phil Krause raised the issue of ensuring the study design/setting has statistical reliability. The size of the study will impact statistical power and so infection rate and number of subjects shedding virus after infection need to be considered.

Finally, Jakob Cramer asked whether the SAC felt CHIM could be used to evaluate broadly protective vaccines and whether CEPI should therefore include CHIM in its BPCV program. Manu Hanon was supportive of this, commenting that measured immune responses might provide data on challenge strains, vaccine candidates and baseline immunity and could therefore infer the breadth of protection.

What criteria would you use to select promising mucosal vaccine candidates for CHIM-based vaccine trials to assess transmission blocking?

In order to identify vaccines that could be most promising, Stanley suggested running an experiment in which subjects are given a parenteral dose of an existing vaccine followed by an intranasal dose and then challenged with SARS-CoV-2. These data can then be compared to the data of those who have been given two parenteral doses in a real-world environment, to see which vaccines show non-inferiority based on administration method. For standardisation, the group felt that these experiments should be done by CEPI rather than an external partner, and use standardised assays and nasal wash methodologies.

Although in agreement with the proposed approach, David Vaughn highlighted what had also been raised in the BPCV plenary session; that access to vaccines for use in such studies is an ongoing issue that needs to be considered.

Which experimental approaches and which parameters would you focus on and use to assess and harmonise mucosal immunity and transmission?

The SAC highlighted that there is relatively little known about protection in the mucosal membranes, and in particular:

- The level and type of response that is necessary to protect against infection and/or transmission
- Persistence of mucosal immunity.

It was also acknowledged that there is huge natural variability in nasal secretions, even within one person over the course of a day for example. As such, the group was aligned on the need to standardize nasal wash methodologies in order to limit variation in results as much as possible.