CEPI SAC meeting summary

Date	Time	Location
Tuesday, 19 July 2022	12:00–15:00 BST	Virtual

SAC attendees

- **Sani Aliyu,** Cambridge University Hospitals Foundation Trust, UK
- **Vineeta Bal,** Indian Institute of Science Education and Research, Pune, IN
- **Alan D. Barrett,** University of Texas, Medical Branch, US
- **Luciana Borio,** Arch Venture Partners, US
- **Paula Bryant,** National Institute of Allergy and Infectious Diseases, National Institutes of Health, US
- **Inger Damon,** Centers for Disease Control and Prevention, US
- **Michel De Wilde,** MDW Consultant, LLC, US
- **Peter Dull,** Bill & Melinda Gates Foundation, US
- **George Gao,** Chinese Center for Disease Control and Prevention, CN
- **Azra Ghani,** Imperial College London, UK
- **Josie Golding,** Wellcome Trust, IE
- **Rebecca Grais,** Epicentre, FR
- **Emmanuel Hanon,** Viome, BE
- **Kent Kester,** IAVI, US
- **Michael King,** University of Virginia, US
- **Phil Krause,** WHO, US
- **Dominique Maugeais,** Independent consultant, FR
- **Krishna Mohan Vadrevu,** Bharat Biotech International, IN
- **Laura A. Palomares Aguilera,** Instituto de Biotecnología, Universidad Nacional Autónoma de México, MX
- **Peter Paradiso,** Paradiso Biologics Consulting, LLC, US
- **Stanley Plotkin,** University of Pennsylvania, US
- **Frances Priddy,** Independent consultant, US
- **Mahmudur Rahman,** GHD|EMPHNET, BD
- **Peter Smith,** London School of Hygiene & Tropical Medicine, UK
- **Stephen Thomas,** SUNY Upstate Medical University, US
- **Michael Watson,** MEVOX & VaxEquity Ltd, UK

Apologies

- **Alash'le Abimiku,** International Research Center of Excellence, Institute of Human Virology, NG
- **Christian Drosten,** Charité – Universitätsmedizin Berlin, DE
- **Ken J. Ishii,** International Vaccine Design Center, The Institute of Medical Science, The University of Tokyo, JP
- **Marc Lipsitch,** Harvard T.H. Chan School of Public Health, US
- **Vasee Moorthy,** WHO, UK
- **Gary Nabel,** ModeX Therapeutics, US
- **Rino Rappuoli,** GSK Vaccines, IT
- **Marco Safadi,** Santa Casa de Sao Paulo School of Medical Sciences, BR
- **Linfa Wang,** Duke-NUS Medical School, SG

CEPI attendees

Speaking

- **Richard Hatchett,** CEO
- **Melanie Saville,** Executive Director, Research and Development
- **Ingrid Kromann,** Acting Executive Director, Manufacturing Network and Supply Chain
- **Rebecca Farkas,** Head of Technology
- **Renske Hesselink,** Senior Scientist, Chemistry Manufacture Controls
- **Gerald Voss,** Consultant
- **In-Kyu Yoon,** Director, Programmes and Innovative Technology

Observing

- **Mike Aviles,** IT Officer
- **Gabrielle Breugelmans,** Director, Epidemiology
- **Carolyn Clark,** Senior Scientist
- **Danielle Craig,** Regulatory Affairs Lead, Americas
- **Sarah Doyle,** SAC and JCG Officer
- **Joe Simmonds-Issler,** Chief of Staff
- **Roice Fulton,** Consultant
- **Nicolas Havalenge,** Consultant
- **Paul Kristiansen,** Director, Laboratory Research and Innovations
- **Stephen Mayhew,** Director of Strategy and Portfolio
- **Marion Motari,** Legal Counsel
- **Mark Polhemus,** Project Leader
- **Sheldon Poujade,** Business Development Lead
- **Kelly Simpson,** Portfolio Officer
- **Nadia Tornieporth,** Consultant

ITEM 1: Welcome and introductions

Richard began the meeting by welcoming attendees and inviting Manu Hanon, Mike King, and Laura Palomares to introduce themselves as the new Chair and Vice Chairs of the SAC.

Richard then provided an overview of the agenda for the meeting, giving his thoughts on the main two topics to be addressed:

1. COVID vaccine portfolio review
    - Richard explained that the SAC would be asked not only to review the current CEPI COVID portfolio, but also to consider the prospects for broadly protective vaccines that could help to move us away from the ongoing cycle of 'chasing variants', noting that, although we are expecting omicron-specific and bivalent vaccines to hit the market shortly, this potentially still leaves us in a vulnerable position with a rapidly and unpredictably evolving virus.
    - He explained that this discussion derives directly from a request from the Board for input on the plausibility and logic of CEPI's plans to develop more broadly protective or enduring vaccines, vaccines to interrupt transmission, and ultimately a pan-coronavirus vaccine.
2. Accelerating vaccine development
    - Richard explained that the second session of the agenda would centre around discussion of platforms that have been validated but also encountered various challenges through the response to COVID-19. He advised that the SAC would be divided into three breakout groups to consider one platform each, brainstorming innovations that could most effectively optimize them for use in a rapid response setting.
    - He explained that this is again in response to requests from the Board for guidance on how much of CEPI's funding over the next five years needs to be invested in validated platforms and advancing them for as many pathogens as possible.

Finally, he acknowledged the current Monkeypox outbreak and advised that, although we would not be able to cover the topic during the present meeting, an additional ad hoc meeting would be scheduled for 29 July.

ITEM 2: Where we are today

Richard provided a brief overview of the growth and re-organization of CEPI, highlighting the recent establishment of a dedicated Manufacturing and Supply Chain division (the importance of which is reflected in the appointment of Mike King as Vice Chair of the SAC), and a small Emergency Preparedness and Response team.

He also summarised the current funding status of CEPI, noting the impressive commitment of USD 1.6Bn received at the resource mobilisation event in March (which contributes to CEPI's USD 3.5Bn 5-year target), but also the gap of USD 1.9Bn that this leaves to be bridged.
He informed the SAC that, as a result of this shortfall, as well as the emergence of other global priorities that may affect international commitment to pandemic preparedness (e.g. military, economic and food crises), CEPI is taking a 'tactical pause' on initiating new calls for proposal, both to consolidate the organisation internally in light of structural changes, and re-consider its priorities.

Lastly, he presented a high-level overview of progress within the CEPI portfolio since the November portfolio review.

In response to Richard's presentation, Peter Dull commented on the notable absence of France, Spain, and Sweden in the list of contributors to CEPI 2.0 to date, and queried whether Richard felt that any

reticence to pledge funds was due to countries wanting to prioritise 'in-house' (national) product development.

Richard acknowledged that there are several regional and national efforts being established that echo and embrace CEPI's 100-day goal and the concept of developing vaccine libraries as a step towards preparedness and that, as a result, the aggregate global investment in pandemic countermeasures is likely to increase; however, in order to avoid redundancy, it is critical that CEPI plays a role in building consensus on the strategic approach of these new organisations and programmes, and facilitating coordination of effort.

ITEM 3: COVID vaccine portfolio review

Melanie began by re-iterating the objectives of the session; to gain advice on how to prioritise investments for COVID-19 in the knowledge that current vaccines are unlikely to be effective long-term solutions. She advised that discussions would centre around:

- how to apply learnings from the existing CEPI portfolio
- the potential of broadly protective SARS-CoV-2 and betacoronavirus vaccines as long-term solutions
- the knowledge and research gaps that CEPI is uniquely positioned to address regarding specific COVID-19 variants
- the potential to advance mucosal transmission blocking vaccines
- the potential application of CHIM in COVID vaccine R&D

To set the scene for the discussion, Melanie showed an overview of CEPI's investments in COVID-19 from an R&D perspective. She then commented on some of the notable successes of the Wave 1 portfolio, but also highlighted that vaccine efficacy of wave 1 candidates against Omicron appears to be waning over time, particularly against less severe disease, indicating that these will not be suitable long-term solutions.

In light of this, Melanie defined the current strategies being employed to work towards broader and more durable protection, which in the most immediate term involves exploration of mix and match heterologous boosting, and then licensure of variant-specific and bivalent vaccines (expected to come to market by Q3 2022). However, this approach (as previously mentioned by Richard) could leave us in the vulnerable position of 'variant chasing' and so, in March 2021, CEPI put out call for proposal for broadly protective SARS-CoV-2 vaccines (aiming for clinical proof of concept by 2022/23) and broadly protective betacoronavirus vaccines (aiming for clinical proof of concept by 2026). There are now 11 broadly protective candidates in the CEPI portfolio (5 SARS-CoV-2 and 4 betacoronavirus), all based on either protein or RNA platforms.

The questions then posed to the SAC were:

1. How do we strike the right balance between conventional strain variation vaccines and broadly protective approaches?
2. Are there gaps in the CEPI portfolio?

Clarification questions

Mike Watson began the discussion by asking three questions:

1. Is CEPI considering DNA vaccines or has it been decided that this is not a viable platform to pursue?
    - Melanie responded that one of first investments CEPI made was in an Inovio DNA vaccine which progressed rapidly; however, the volumes that could be produced were a huge limitation as was the need for a specific delivery device and so, although CEPI still has investments with them for other vaccines, at this time the leadership team (LT) does not feel that DNA is best suited large-scale pandemic response.

2. Rather than pursuing bivalent vaccines, has CEPI considered the possibility of administering multiple vaccines?
    - Melanie explained that CEPI is not specifically funding any bivalent approaches and so this sits outside of the current scope of the organisation.
3. Is there any ongoing investigation into the impact of COVID-19 infection on the immunity of vaccinated individuals? Data suggest that vaccination followed by infection provides greater depth and breadth of protection and so when considering what 'better' looks like in the context of developing novel COVID vaccines, this may be an important baseline to have.
    - Melanie confirmed that several analyses have been done on this and CEPI is planning to fund studies of vaccination strategies in previously infected individuals.

Question 1: Striking the right balance between variant-specific and broadly protective vaccines

The SAC was aligned on the fact that CEPI should not be involved in the chasing of variants, which they described as a worrying trend analogized to the act of chasing a train that's left the station – by the time a variant-specific vaccine reaches the shelves, a new variant will have taken over as the dominant circulating virus.
CEPI should instead focus its efforts on developing broadly protective vaccines; however, recognising that these will take some time to develop, it was acknowledged that a variant-specific approach cannot be entirely discounted as it may still serve a purpose in the short term, bridging the gap between the waning efficacy of wave 1 regimens and the availability of broadly protective vaccines. Azra Ghani commented that understanding this timeline would therefore be critical for determining how much effort needs to be put into strain-specific vaccines, and the group suggested that CEPI should play some role in co-ordinating the scale of this response within the scientific community. Peter Paradiso built on this suggestion, commenting that CEPI may also want to consider supporting prediction of what the next variants might be.

- Melanie explained that we hope to see Phase I/IIa trial data from CEPI's broadly protective portfolio candidates as soon as 2023, but that realistically distribution will not happen until a couple of years after this.
- Melanie also explained that the Board has queried why CEPI is not working with more experienced developers on its broadly protective candidates, as partnerships with less experienced facilities could cause challenges or delays. It has been explained to the Board that the novel approaches that these broadly protective candidates are based on are currently in the hands of more academic groups but that the LT acknowledges there will be a need to match these academic institutions with more experienced developers as things move forward.
- In response to this, Mike King suggested that earlier support for these facilities may actually be beneficial, or even required, in the form investment in the development of robust production processes, as the academic institutions may lack the experience required to make CTM consistently, and standardisation will be essential to the success of the candidates.

Recommendation: CEPI and SAC to align on the scale of the need for variant specific vaccines based on anticipated timelines for broadly protective vaccine development.
Recommendation: CEPI to develop external comms/guidance on limiting variant-specific vaccine development and prioritising BP approaches.
Recommendation: CEPI to consider what investments could be made to support the development of robust production processes for the broadly protective vaccine candidates in development with academic institutions.

In reference to the session objective of 'gaining advice on how to prioritise investments for COVID-19', Phil Krause asked whether the SAC should be considering this ask purely in the context of science and research, or whether CEPI's remit extends to infrastructure building.

In response to this, Peter Paradiso highlighted existing efforts to coordinate CEPI, the NIH and the NAID around broadly protective approaches, summarising that the NIH tends to focus on more basic

science approaches with limited involvement in final product production, whereas CEPI investments pay much more attention to CMC.
He briefly summarised a meeting held between the groups two weeks prior to the SAC, which focused on identifying target product profiles and included discussion on different arms of the immune system including memory B cells and T cell responses, how to look for correlates of immunity, animal model studies and assay development.

Question 2: Gaps in the CEPI portfolio

B cell memory

Stanley Plotkin commented that B Cell memory has been a major neglected area of research for COVID-19 vaccines, and will likely cause challenges for other respiratory infections in the future, and so asked whether any investigation was being done in this area.

- Melanie confirmed that this is not currently being explored by CEPI but agreed that it is something that needs greater attention.
- George Gao raised the point that the Hepatitis B vaccine is a protein-based vaccine, and B Cell memory lasts for decades, so it is unclear why protein-based COVID vaccines do not elicit the same memory response. He re-iterated that this should be a critical area of research for CEPI as, once solved, we will be in a much better position for strong vaccine design.

Recommendation: CEPI to consider what investments could be made to investigate long-term B cell memory to support vaccine design for enhanced durability

T cell response assessment to support broadly protective vaccine evaluation

Vineeta Bal advised that, for correlates of protection to be rapidly analysable, significant improvement is needed in T cell response assessment approaches. T cell responses have been found to be much longer lasting and broadly protective relative to our current knowledge of the duration and breadth of protection of neutralizing antibodies. As such, platform approaches to the rapid evaluation of T cell responses would be welcomed.

Recommendation: CEPI to consider what investments could be made to help improve rapid analysis of T cell responses.

Protein platform optimisation

Mike Watson expressed support for CEPI investigating how to optimise protein vaccine platforms, noting that there are still many elements of protein-based vaccines that need to be 'locked down' before he feels that proteins can truly be defined as a platform, in the same sense as RNA now can. Manu advised that this is indeed a priority for CEPI and that the next session would include discussion on innovations that could be pursued in order to achieve this.

Mucosal transmission blocking vaccines

Following this initial discussion, Melanie presented a brief overview of the coronavirus mucosal vaccine landscape.

She advised that the concept of mucosal vaccines is often raised in relation to respiratory viruses, and that CEPI is now keen to explore what the value of intranasal delivery might be in the context of COVID.
She briefly outlined the known challenges of the approach, including but not limited to; the persistence of antigen presentation at the mucosal surface, stability to withstand antigen clearance, and the need for household transmission studies with a high secondary attack rate, and then informed the SAC of the 3 mucosally-delivered vaccines that are currently in the CEPI portfolio.

The SAC generally expressed strong support for investigation into intranasal vaccines, with Stanley Plotkin stating that the concept of how to induce mucosal immunity represents a huge knowledge gap,

and is something that is critical to the future of combatting respiratory agents. However, the SAC had differing opinions on what CEPI's involvement should look like:

Peter Dull suggested that CEPI may be uniquely positioned to support with projects related to mucosal vaccine de-risking (i.e. understanding mucosal immunity or funding efficacy trials), reminding the group that there was a huge desire from the community for intranasal vaccine research around COVID, but that many trials were unable to progress as researchers didn't have the tools to de-risk.

Mahmudur Rahman advised CEPI to be mindful if pursuing this approach in the context of COVID-19, that although current circulating variants target the upper respiratory tract mucosa, previous variants targeted the lower respiratory tract, and so it will be important to assess how effective any intranasally-delivered vaccines would be against previous variants.

Phil Krause, however, offered an alternative view, querying whether investment in intranasal vaccines would really be viable as an option for COVID at all, given they would not come to market for a long time, and suggested that it might be prudent instead to investigate intranasal vaccines for other respiratory targets.

Manu Hanon suggested that perhaps intranasal delivery could be employed for some of the broadly protective coronavirus vaccines.

Before providing further guidance, the SAC asked for greater clarity on what CEPI hopes to achieve with the 3 intranasal candidates currently in the portfolio.

Recommendation: CEPI to further develop objectives and targets of intranasal vaccine research projects.

The potential role of CHIM in coronavirus vaccine development

Melanie lastly presented a short summary of the potential role of controlled human infection models (CHIM) in coronavirus vaccine development and asked for the SAC's opinions on whether CEPI should invest in CHIM for the evaluation of transmission blocking and broadly protective COVID vaccines. She noted that the general perception is that regulators are not ready to accept CHIM yet as a pivotal methodology to get to licensure, but that opportunities exist to explore this.

Stanley Plotkin expressed strong support for investment in CHIM and urged CEPI to visit a new CHIM facility that has been established in Belgium, led by Pierre Vandamme and Arnaud Marchant. He described the facility as extraordinary and recommended that CEPI considers how they could take advantage of existing facilities such as this to expand knowledge not just on preventing disease but preventing infection.

In line with his earlier comment requesting clarity on the objectives of CEPI's research into intranasal vaccines, Phil Krause also asked for more specificity of CEPI's goals for CHIM. His suggestion was to think about what the library of challenge strains should look like at any one time, and explore how CEPI could facilitate making these available.

Recommendation: CEPI to further develop objectives for CHIM.

ITEM 4: Key opportunities for, and barriers to, achieving accelerated vaccine development

Manu welcomed back the attendees after a short break and began by outlining the objectives of the session; to brainstorm innovations that could most effectively help to overcome the challenges, or

further leverage positive characteristics, of three critical platforms (mRNA, adenovectors, proteins) in order to optimize them for use in a rapid response setting.
He advised that innovations would be grouped into the following categories, and could be related to speed, scale, access or safety:

- Pre-clinical
- Clinical
- Regulatory
- Manufacturing

mRNA

In-Kyu gave the breakout group a brief summary of the perceived benefits and challenges of mRNA platforms, and asked participants to advise of anything further that they felt should be included. The group's thoughts are summarised below:

Additional benefits

- the availability of an mRNA master file
- potential to genericise RNA

Additional challenges

- time needed to identify an appropriate antigen – it was commented that we were lucky with COVID, having such an immunodominant antigen that worked but we may not be so lucky in future
- durability (although acknowledging that the lack of durability seen with COVID vaccines has not been proven to be platform-related and could be caused by the spike protein, or both)
- access to lipids for LNPs – supply or IP
- if broadly protective vaccines are not successful, we may need to resort to multivalent approaches, and the higher doses of mRNA and LNP required for this may present reactogenicity challenges

Paula Bryant also suggested an amendment to one of the existing points, suggesting that any cell banks created should be derived from human lines rather than E.Coli in order to be perceived as credible by the regulatory bodies.

The group then discussed what innovations could be explored in order to minimise the impact of these challenges identified. Discussions have been summarised in the table below:

	Challenges	Innovations
Pre-clinical	• Some pathogens not compatible with mRNA e.g. monkeypox • Time to identifying, design and develop an appropriate antigen could slow down development (not an issue with COVID due to previous experience with class I viral fusion proteins and coronaviruses) • Access to lipids • Lack of clarity on what determines a durable response	• Invest in libraries ahead of outbreaks (prototype pathogen approach), generation of toxicity data and clinical trial lots
Clinical	• Dose finding – how can we limit the time that this takes? • Regulators are starting to require extensive screening/monitoring for	• Establish criteria for moving straight to effectiveness studies • CHIM

	adverse events in early studies which is extending trial lengths • Thermostability	
Regulatory		
Manufacturing	• Ensuring there is enough demand for mRNA vaccines to keep manufacturing capacity alive between outbreaks	• Methods to scale up manufacturing extremely fast, or occupy facilities with e.g. flu mRNA vaccine production
Ease of final vaccine storage, distribution and admin.	• Storing frozen produces a bottleneck to fast administration in a pandemic setting	• Investigate development of fully liquid mRNA vaccines • Intranasal administration
Enabling global access		• De-centralization of vaccine production and innovation to lower COGs

Protein

Gerald gave the breakout group a brief summary of the perceived benefits and challenges of protein platforms which were broadly agreed upon by the participants.

The group then discussed what innovations could be explored in order to minimise the impact of challenges identified. Discussions have been summarised in the table below, and includes additional comments received after the meeting:

	Challenges	Innovations
Pre-clinical	• Need to do extensive animal studies for things like toxicology despite extensive evidence to suggest proteins are a safe platform (link to regulatory requirements) – however, need to recognize effects of adjuvants • Evaluation of non-IM subunit vaccines	• Masterfiles of adjuvants • More accessible adjuvant strategy to prevent hoarding like seen in COVID-19
Clinical	• Persistence of immune response – peak and levelling off over time • Need to assess other arms of the immune system e.g., cellular responses • Bed-side mixing of two-vial vaccines for clinical trials may prevent conducting trials at certain sites	• Establish milestones that can be used across different candidates / required for each step. Avoids duplication • Two-vial presentation of CTM
Regulatory	• Regulators not always comfortable with sites manufacturing multiple product types • Advantage: ○ Familiar platform for regulators but this is extending to other platforms	

Manufacturing	• Cheaper to manufacture at volume but adjuvants can increase costs • Relatively slow during COVID – need to understand drivers for this • Nanoparticles remain very challenging to manufacture consistently with many still in exploratory/academic phases • Advantage: ○ Same facilities could also manufacture biopharma drugs when vaccines are not needed – useful consideration for LMICs	• Conduct a cost / benefit analysis- look at timelines for approval for different platforms including non-CEPI candidates (lessons learned from COVID-19) • Transient transfection as an accelerator • Need for pre-investments into processes that enable line of sight from CTM to commercial manufacturing

Ease of final vaccine storage, distribution and admin.	• Slow to market but overall profile is very strong and comparable to mRNA (but needs evaluation to assess durability, efficacy etc from R&D)
	• Advantage:
	  ○ Temperature for storage more suitable for global distribution
	  ○ Generally good thermostability
	  ○ Shelf life typically longer than mRNA
		• Opportunities to continue to improve thermostability, packaging etc

Enabling global access	• Advantages
	  ○ Regional manufacturing established
	  ○ Good safety profile, provokes less vaccine hesitancy in the population – proteins may be more suitable for global access
	  ○ Goods needed to manufacture are widely available and so less likely to be a bottleneck in terms of supplies	

Adenovector

Rebecca gave the breakout group a brief summary of the perceived benefits and challenges of adenovector platforms, and asked participants to advise of anything further that they felt should be included.

The group then discussed what innovations could be explored to minimise the impact of these challenges identified. Discussions have been summarised in the table below:

	Challenges	Innovations
Pre-clinical	• Comparative efficacy with mRNA not fully clear – potentially disproportionate investment in mRNA in emergent situations	• Pre-investment in adeno platform development • Targeted approaches to identify toxicity study and other pre-clinical objectives
Clinical	• Balancing time to market versus safety profile e.g. AZ COVID-19	• Focus on safety profile characterization

	• Dosing regimen to obtain high efficacy unclear • Pre-existing immunity for extant viral subsets – effect on boosting strategy and outcomes? • Likeliness of need for 2 doses to achieve strong efficacy - Interval between doses of particular importance (especially in pandemic context)	• Route of administration e.g. mucosal, intradermal or microarray • Address key clinical objectives on a whole-of-platform basis • Consider ratio pf investment in new generation vs reliance on dataset for contemporary vaccines
Regulatory	• Overcoming confidence barriers to platform • Safety profile challenges, particularly in LMICs	
Manufacturing	• Reagent/sera shortages	• Master seed development • NRVV specific platform investments through R&D cycle • Can CEPI influence availability and import clearances? • High yield • Mammalian cell culture utility? (although still slower than mRNA)
Ease of final vaccine storage, distribution and admin.	• Storage at 2-8°C	• High yield • Administration route innovations specific to platform
Enabling global access	• Tech transfer considerations • Vaccine hesitancy • Emerging variants demanding rapid response and logistical integrity • Cost • Global manufacturing capability potential inequity	• Potential to develop a more globally connected manufacturing infrastructure – equitable distribution of platform hubs? (ex. Africa mRNA hubs)

Overall, it was agreed that these discussions were rich, but time was limited and, as such, clear recommendations are yet to be provided.

Recommendation: CEPI to follow up with SAC to ask for more specific guidance on how to translate the topline outcomes from the brainstorming discussions into tangible actions

ITEM 5: Meeting summary and closing statements

Manu thanked the SAC for their attendance and contributions, which was echoed by Vice-Chairs Mike King and Laura Palomares, and the CEPI leadership team.
Melanie then outlined next steps, indicating that a summary report would be shared in the coming weeks, and that an invitation for an ad hoc discussion on Monkeypox would be sent imminently.