Coalition for Epidemic Preparedness Innovations

CEPI Scientific Advisory Committee (SAC) Teleconference
September 12, 2018
Washington DC, U.S. and teleconference

SUMMARY FROM SAC PROCEEDINGS (CEPI/SAC *TC 18.3*)

The following Scientific Advisory Committee members participated:

Committee members		**Invited and CEPI**
Present • Helen Rees (Chairperson) • James Robinson (co-chair) • Alash'le Abimiku • Connie Schmaljohn • Inger Damon • John Edmunds • Michel De Wilde • Myron Levine • Paula Bryant • Peter Smith • Phil Krause • Ralf Clemens • Stanley Plotkin • Yves Lévy ***Apologies***: • Christian Bréchot • Christian Happi • Daniel Brasseur • Delese Mimi Darko • George Fu Gao • Kathleeen Neuzil • Kenji Shibuya • Penny Heaton • Thomas Kariuki	**Non voting members** • Ali Allouche, Takeda • Jean Lang, Sanofi • Johan van Hoof, J&J • Kathrin Jansen, Pfizer • Vasee Sathiyamoorthy, WHO	***Invited:*** • Amy Jenkins, DARPA • Charlie Weller, WT • David Vaugh, BMGF • Jeremy Blum, BMGF • Matt Hepburn, DARPA • Mike Osterholm, CIDRAP • Peter Dull, BMGF • Wolfgang Leitner, NIAID • Ruth Faden, PREVENT • Ruth Karron, PREVENT ***CEPI Secretariat***: • Richard Hatchett • Gunnstein Norheim • Melanie Saville • Hinta Meijerink • Nicole Lurie • Dawn O'Connell • Nora Indrehus • Shannon Quinnon • Raul Gomez • Joe Simmonds

Notes to readers

- Pre-read documents for the meeting were shared ahead of the meeting. Slides are found here.
- This meeting was originally planned in Atlanta, but due to hurricane warnings it was moved to Washington DC and for most attendees conducted as a telecon.
- The main agenda item for the meeting was to discuss exploration of new investment areas.
- Meeting rapporteur: Raul Gomez, CEPI Secretariat

1. Exploration of new investment areas

Introduction (Richard Hatchett)

CEPIs CEO gave an overview of the current funding portfolio and the context for this meeting.

One of CEPIs strategic goals is sustainability.

Currently: Total amount funded through CfP1 and CfP2 currently stands at around 430 million USD. The "Enabling Science" elements under Vaccine Science are funded for the next 5 years.

What has changed since CEPI's first strategy in 2016?

Assumptions in 2016	Developments
CEPI to take a gap filling role in Ebola.	CEPI has been part of a working group to identify gaps leading to licensure. New outbreaks.
Zika is well funded and likely to have good potential in the market. No need for CEPI involvement.	Funding has declined.
Chikungunya likely has a potential market.	Chikungunya vaccines now eligible for FDA Priority Review Voucher
CEPI should not focus on Phase III studies.	WHO Priority Pathogens list has shifted slightly.

The main objective of this SAC meeting is to explore new investment areas. The reason is that the funding opportunities are widening, with potentially 90 million euro from the EC to become available for new projects in emerging infectious diseases (30 mEUR in 2019 and 60 mEUR in 2020). This is a good time to identify areas of investment 5 yrs down the road. Considerations for new investments, new areas to be discussed, and questions for the SAC roundtable discussion were presented (slides 9, 10 & 11, respectively).

The Chair asked if CEPI had enough resources to co-fund any EC-funded projects and the answer was affirmative. The WHO representative asked if there were requirements for funds to be spent in Europe and the answer was no. The only requirements to access the incoming EC funding are that the projects be new and that they be co-funded at 70:30 (EC:CEPI) ratio.

Priority Pathogens Vaccine Portfolio

The Director of Vaccine Development Melanie Saville gave an overview of the current Priority Pathogens Vaccine Portfolio.

Currently, contracts have been signed with 6 partners for 8 vaccines in total: 4 for Lassa, 3 for MERS and 1 for Nipah. Negotiations are underway and CEPI anticipates to have more partners for CfP1 and CfP2 implementation.

The Lassa portfolio (slide 15) consists of 6 candidates (5 viral vectors and one DNA approach); the first first-in-human (FIH) trials will take place in 1QY2019. The MERS CoV portfolio (slide 16) consists of 4 candidates (3 viral vectors and one DNA approach), with three FIH trials already ongoing. The Nipah portfolio (slide 17) consists of 4 candidates (3 viral vector and one adjuvanted protein approach), with the first FIH trials scheduled for 1QY2019.

Additional vaccines against priority pathogens are likely to be funded through the CfP2, increasing also the portfolio of technologies with over 30 vaccine candidates of which 20 against WHO R&D Blueprint pathogens.

Roundtable discussion:

What is the priority approach in bringing vaccines forward, and what data will be used to select the best candidates to move to the clinic? Experience from BARDA and other programs suggests it that due to attrition it is best to have three to six programs funded to end up with a single licensed product. CEPI does not plan to down-select candidates right after Phase I; instead, if several products make it past pre-defined stage-gates, then they would be down-selected in a portfolio review.

A question was raised as to why CEPI's Nipah approach is so focused on Bangladesh, and why not include sites in India given the recent outbreak. Response from Secretariat was that we are exploring including sites in India as well with the developers and has a flexible approach.

Results from Request for Information (RfI) on Lassa, MERS, Nipah and Chikungunya vaccines

Gerard Cunningham (consultant to CEPI) presented results from the RfI. The purpose of the exercise was to identify any vaccine candidates for Lassa, MERS or Nipah that could increase the likelihood for achieving CEPIs Strategic objective 1 by 2022. The main conclusion from the RfI was that there are no additional, compelling opportunities for funding that are not already being funded/considered by CEPI in the current portfolio for Lassa, MERS and Nipah.

Roundtable discussion:

For Nipah, the over representation of vectored-approaches is a concern. Should CEPI not actively seek other platforms/approaches? What about RNA or pre-stabilized fusion proteins? University of Queensland is proposing a molecular clamp approach to stabilize glycoproteins for MERS, RSV and flu, but they also have some preliminary work on Nipah and perhaps could be approached.

Chikungunya

Should CEPI support development of a Chikungunya vaccine? Chikungunya originally ranked 4th in priority in the SAC's 2016 list, and high disease burden was considered (slide 53). A CEPI Chikungunya workshop was co-organized with DBT & PATH in February 2018, which highlighted many of the gaps and areas of opportunity. A draft report of the meeting was provided in the pre-read materials for this SAC.

A request for information (RfI) to map interested developers was conducted in July 2018 and the results were presented (slides 54-64). The main conclusion is that the pipeline is well matured, with several candidates are advanced in development and ready/moving into phase 3, supplemented by multiple pre-clinical stage candidates and ready to move into phase I. Implications for CEPI: CEPI could provide co-funding, either of Phase III with EC co-funding, or fund phase I-ready program*s.*

Stanley Plotkin gave an overview on the epidemiology and human impact of Chikungunya on the global population, with 217 thousand cases worldwide. The correlates of protection (slide 72) were highlighted, with IgG3 antibodies shown to be the main neutralizing and protective antibodies (as demonstrated by passive transfer challenge studies), while T cell responses may be detrimental and responsible for disease symptoms. Again, the vaccine pipeline is good; and in Stanley's view, there are three leading candidates (slide 74).

Roundtable discussion:

Comments/Questions to the SAC were: there are several Chikungunya vaccine candidates that could be put into Phase III rapidly, with a high probability of success. This is a disease that causes sequelae and a vaccine funded by CEPI could have important impact and provide a rather short-term success (low hanging fruit). Chikungunya is not on the current WHO priority list category of urgent action, but that doesn't mean it shouldn't be funded. The notion "Phase III trial" was, due to unpredictable and short nature of Chikungunya outbreaks, interpreted as a safety, immunogenicity and immunobridging trial.

There was no unison view in regard to CEPI investing in Chikungunya vaccines. On the positive side, the feasibility of the vaccine development (pipeline, mechanism of protection, disease burden) as well as the possibility of CEPI taking part in an achievement by 2022, whereas others expressed concern that Phase III studies could be extremely challenging because Chikungunya outbreaks are very explosive and unpredictable, and suggested going for the FDA Animal Rule rather than a Phase III. The CEPI Delhi workshop was again referenced. A way to predict outbreaks would be by surveys of the vector. From the regulatory perspective, it would be important to pay attention to the Animal Rule, conduct passive transfer studies and see if this streamlines licensure/post-licensure.

Other questions and answers were raised: Why is Chikungunya now listed as a lower priority for research in the WHO priority pathogen list as compared to the 2016 list? A closer look into the methodology should be taken. What would make Chikungunya different from Zika, i.e. why invest in a Chikungunya and not in a Zika vaccine? What is the added value of CEPI funding this, i.e. what would happen if CEPI did not fund it? Is there a commercial market for Chikungunya vaccines? The elements will be further discussed in the forthcoming SAC Roundtable session.

WHO R&D Roadmap priorities as investment areas

An overview was given by Vasee Moorthy from WHO & Mike Osterholm from CIDRAP, who had worked closely developing the WHO R&D roadmaps for Lassa, MERS and Nipah. The WHO makes efforts not to change its priority diseases too frequently. There is a generic methodology applied to each priority disease for the Roadmap development, for example, Baseline Situation Analysis (background papers describing each pathogen & disease) are drafted, while pathogen-specific taskforces are created. New developments with relevance to CEPI were highlighted (slide 103): Nigeria, the DRC and India have approached WHO for assistance through the R&D Blueprint during outbreaks; and Ebola vaccines have been/are being administered under the R&D Blueprint.

Strategic goals and research priorities were presented for the three CEPI priority diseases (slides 79-95), with Lessons Learned (slide 95) highlighted during the presentation. In the Roundtable discussion, the need for a One Health Approach was expressed.

Gene-encoded antibodies

Matt Hepburn & Amy Jenkins were invited to present an overview of DARPA's work on gene-encoded antibodies (slides 104-120). DARPA has niche role in being able to take on early-stage, high-risk vaccine projects, de-risk the technology, and transfer them to other partners (i.e. potentially CEPI). The Pandemic Prevention Platform (P3, slide 110) was highlighted. All studies rely on first taking convalescent patient sera, getting the sequence of (protective) antibodies, and then administer the corresponding genes (in DNA or mRNA format) to express antibodies in vivo in a relatively short time (within days). Approaches from Duke University (anti-flu and anti-Chikungunya abs in mRNA expression cassette), MedImmune (mRNA, DNA & AAV platforms), Vanderbilt University (mRNA in cationic emulsion), and Abcellera (abs from several species encoded in DNA) were mentioned. Studies on Chik (Moderna) have entered Phase I. Potential collaborations with CEPI were highlighted at the end (slide 120).

Pervin Anklesaria and other from BMGF gave an overview of how the Foundation is also supporting this area of investment. The goal is not to replace a vaccine, but to provide an alternative intervention. The main target pathogen has been HIV and features of a potential TPP for that pathogen were outlined (slide 122). The BMGF portfolio (slide 123) consists of 7 products at very early stages, with 2 entering clinical trials. The gaps for this platform were briefly described (slide 124).

Roundtable discussion:

Are monoclonal antibodies part of CEPIs mission/mandate? CEPI does not fund therapeutics as part of its remit. Nonetheless, "vaccine-like" products or technologies can be pursued to buy time in case of an outbreak/epidemic.

What to do when etiologic agent of an outbreak is not known? There are groups working on how to isolate new, unknown viruses.

Strength of the approach: high and rapid antibody concentrations are achieved in vivo in animals.

To be followed up in the SAC Roundtable session.

Adjuvants

CEPI is exploring two scenarios with the SAC: (1) accessing licensed adjuvants for non-profit use in Emerging Infectious Diseases, and/or (2) funding development of unlicensed adjuvant systems.

To inform the discussion, Wolfgang Leitner, NIAID, was invited to give an overview of their Adjuvant Programs. A long term objective of this program is to build an "Adjuvant Toolbox" allowing for antigens and adjuvants to be matched, as described by the NIAID Strategic Plan for Research on Vaccine Adjuvants. Recent developments in the field were outlined (slide 134) with Inulin (Advax) being the most advanced product in NIAIDs adjuvant portfolio (slide 137).

Roundtable discussion:

How do you see CEPI investing in adjuvants? CEPI has a number of recombinant vaccines that would require adjuvants and we would give preference to licensed/commercial adjuvants, but with openness to pursue new adjuvants that may promote dose-sparing (reduce the number of doses to achieve protective immunity in an outbreak) or antigen sparing. CEPI should consider approaching well tested adjuvants (e.g. GSK for its adjuvant portfolio, in particular ASO1B). From the WHO perspective, pursuing adjuvants that have not been licensed would not be recommended.

Sustainable Manufacturing

Patrick Florent, consultant to CEPI/GSK presented sustainable manufacturing as an area of investment addressing CEPIs Sustainability Strategic Objective (slides 167-173). A small working group including representatives from the DCVMN, GAVI, UNICEF and large pharmaceutical manufacturers is being formed to advice on solutions for long-term sustainability issues. The group will give recommendations to the CEPI Board in December. Questions to the SAC were posed (slide 173).

Roundtable discussion:

There are many considerations and questions that need to be weighed before making a conclusion or recommendation. Is there a financial envelope or limit attached to these investments? What are the time considerations, 3 years from now? Do we want to achieve continuous production of vaccines, or

just stockpiles and replenishing stockpiles for sporadic outbreaks? What are the expected demand and the shelf life for specific products to be considered for sustainable manufacturing?

2. Pregnant Women and vaccines against emerging epidemic threats (PREVENT)

Ruth Karron gave an overview of the PREVENT program and the challenges associated with maternal immunization (slides 174-185). The aim would be to shift the presumption to inclusion of pregnant women in clinical trials. PREVENT has 22 recommendations, out of which five are very relevant to CEPI. Of these, three were highlighted: Recommendation 7, suitability for use in pregnancy should be considered; Recommendation 9, conduct non-clinical studies early, i.e. reproductive toxicology studies; and Recommendation 12, to assume pregnancies will occur.

Roundtable discussion:

There are theoretical possibilities of risks for a live attenuated vaccine to be used in pregnancy, but these concerns should be weighed against the risks of *not* vaccinating a pregnant woman (distinguish between the R&D scenario and the real life/vaccine delivery setting). An example would be the Ebola case. The need to include social/behavioural specialists when considering this area of investment was mentioned. The bottom line for PREVENT is to change the default position. One challenge would be to involve regulators to understand their role; for example, what was the evidence and process by the DRC ministry of health/regulatory authorities that formed the decision that pregnant women not be vaccinated against Ebola.

3. Closing and next steps

Topics not covered due to time limitations were: Update on CfP2 (Melanie Saville), Update on Epidemiology studies for Lassa update (Hinta Meijerink) and Rapid Outbreak Response (Nicole Lurie).

A follow-up session for the SAC is planned for 20 September, 2018, with the purpose of a concluding advice from SAC to the Secretariat to guide its process to suggest new investment areas to the CEPI Board in October 2018.