Controlled Human Infection Models for Beta-Coronaviruses

Call for Proposals

The Coalition for Epidemic Preparedness Innovations (CEPI) is a global partnership between public, private, philanthropic, and civil society organisations whose vision is to create a world where epidemics and pandemics are no longer a threat to humanity. CEPI is working to achieve this vision by accelerating development of vaccines against emerging infectious diseases with a view to the ultimate licensure of these products and use in an emergency. It is an international non-profit association, established to develop vaccines to prevent and respond to future epidemics and to secure access to such products for the populations who need them.

CEPI is pleased to announce a Call for Proposals (CfP) with the aim to build a consortium to conduct Controlled Human Infection Models (CHIM) for betacoronaviruses and to perform vaccine trials using the established CHIM. The program will be co-funded by the European Union within the framework of Horizon Europe. This document describes the scope, requirements, and processes for proposal submission, review, and selection for funding.

CEPI invites applicants to submit proposals for funding. Detailed plans for the production and release of virus challenge stocks, approach for defining human challenge infection models, conducting vaccine trials using CHIM and describing mucosal immune monitoring concepts and data science projects should be included in the application. CEPI expects to fund up to two consortia. This is a global CfP with no geographical restrictions for applicants. Projects must be completed within 5 years starting from January 2024. If you are planning to submit, please request an application no later than 20 August 2023. The submission deadline for applications for the BetaCoVCHIM CfP is Friday 1 September 2023 17:00 CET.

I. Background

The SARS-CoV-2 pandemic was a public health crisis that caused unprecedented disruption to humanity. Previous epidemics caused by other betacoronaviruses, SARS-CoV-1 and MERS, have also resulted in significant morbidity, mortality, and adverse socio-economic consequences. Safe and effective vaccines, in conjunction with other public health measures, will help prevent further loss of life and economic disruption caused by betacoronaviruses and their variant forms. A development program for broadly protective coronavirus (BPCV) vaccines was initiated by CEPI in 2021. Selected awardees have focused efforts on developing vaccines against SARS-CoV-2 variants, sarbecovirus, and coronaviruses in general. At present, these CEPI-funded vaccine candidates are in the pre-clinical development phase and early stages of clinical trials. Given the continued spread of SARS-CoV-2 in the global

population and the potential risk of zoonotic emergence of other coronaviruses and respiratory viruses, understanding mucosal-mediated protection from infection and transmission is an emerging research priority.

Mucosal immunity is likely to be crucial for the prevention of infections by and transmission of respiratory pathogens. Vaccines that block infection or human-to-human transmission can limit viral spread in the population and significantly impact the epidemic curve during outbreaks. An increasing number of COVID-19 vaccine candidates which target mucosal immunity to prevent infection and transmission are currently in development. However, harmonised methods and strategies for assessing these vaccines have not been established. Major challenges include:

i. Lack of harmonised and validated research models to evaluate the efficacy of novel mucosal-targeting vaccines;
ii. Lack of informative, standardised, and qualified assays to monitor mucosal immunity;
iii. Lack of immune markers associated with reduced risk/prevention of infection and transmission; and
iv. Lack of licensed COVID-19 vaccines that prevent infection and viral spread in the human population.

CHIM studies to investigate vaccine-induced and mucosal immune responses are of public health importance as they can provide evidence on the prevention of infection and transmission that would otherwise be difficult or impossible to obtain from conventional clinical trials. CHIM studies involve the deliberate infection of healthy volunteers under tightly controlled safety conditions and have distinct advantages over field studies. CHIM studies could significantly contribute to generate data for novel broadly protecting vaccine candidates against pan-sarbecovirus or pan-beta-coronavirus as well as for mucosal vaccines to block infection with SARS-CoV-2. CEPI aims to support networks and collaborations in this research area.

This is a jointly funded CfP resulting from the collaboration between CEPI and the European Union's Horizon Europe program. Thanks to generous co-funding from the European Union, CEPI has now the possibility to present this funding opportunity for a betacoronavirus CHIM consortium.

2. Objectives

CEPI is seeking to identify awardees able to prepare, perform, and analyse CHIM trials in support of betacoronavirus vaccine programs. Lead awardees should be experienced to conduct human challenge infection studies and/or vaccine clinical trials. These studies may include the SARS-CoV-2 variants or seasonal betacoronaviruses. Vaccine candidates that primarily target mucosal immunity will be prioritized. CEPI is expecting willingness by the lead partner to coordinate the different partners within the consortium.

The CfP will fund up to two consortia with the aim to establish networks, processes, and procedures to conduct CHIM at a high level of safety, quality, reliability, and reproducibility. The consortium/consortia should represent a multi-country network and cover the following objectives in their programs:

- Build a collaborative network/consortium, based on excellence, innovation, and agility, to develop coronavirus CHIM for testing vaccines, especially mucosal immunity monitoring approaches. Establish a network of experts and clinical sites to conduct harmonised CHIM and CHIM-based vaccine trials at a high level of safety, quality, and reliability.
- The appointment of an independent Ethics Board by each contracted consortium is considered necessary to ensure compliance with EU ethical standards and regulations in all research projects involving human subjects. Note that all clinical activities must be conducted in accordance with the fundamental ethical principles.
- Lead partner needs to develop concepts to maintain efficient, productive, and constructive communication with relevant internal and external stakeholders. CEPI expects awardees to collaborate and communicate closely with national regulatory and ethics committee authorities and regional public health organisations.
- The Lead Partner must develop a plan for record keeping and regular financial reporting to CEPI, including preparation of subcontractors and sub-subcontractors' financial reports for internal and external audits.
- Develop a strategic concept to harmonise selection, isolation, growing characterisation, production, and release of human virus challenge strains (SARS-CoV-2 variants, betacoronaviruses). Innovative approaches to accelerate the manufacture and release of virus stocks are desirable.
- Define and establish harmonised procedures for betacoronavirus CHIM in non-naïve individuals. An attack rate of at least 70% is desirable. Define criteria for volunteer selection based on their immunological profile and other characteristics.
- Conduct challenge vaccine trials based on CHIM to evaluate vaccine-induced mucosal immunity and the potential of candidate vaccines to reduce or prevent infection and transmission.
- Develop harmonised assays and criteria for monitoring mucosal-mediated immunity and transmission-blocking potential induced by vaccines. Establish and conduct a mucosal immune monitoring panel with the goal to develop guidelines for measuring vaccine-induced mucosal immune responses.
- Develop concepts and methods to analyse and determine which immune markers are associated with vaccine-induced transmission blocking potential. Evaluate the strategies of finding correlates/surrogate markers.
- Develop methods to disentangle high-dimensional data regarding vaccine-induced immune responses for evaluation and characterization of immunological signatures associated with protection against infection and/or transmission (*e.g.* viral shedding).
- Develop strategies for using simulation models to assess the impact of vaccination on larger populations using data collected during the vaccine trials.
- Develop concepts to use appropriate statistical methodology.
- Evaluate data and identify immune markers, immune signatures, and potential correlates of protection against prevention of infection/transmission.
- Develop an ethical framework and a streamlined ethics review process.
- Develop strategies to sustain the consortia beyond the funding period, educate staff at new study sites, and connect globally via workshops or conferences.
- Advance communication and education in terms of community engagement.
- Develop strategies and infrastructure for sharing reagents and procedures to harmonise studies.

- Disseminate results and concepts through publications in open access scientific journals.

3. Scope

The scope of this CfP includes CHIM activities to support CEPI in the area of vaccines that target mucosal immune responses against betacoronaviruses, including SARS-CoV-2. These mucosal vaccines may have the potential to reduce the risk of infection and transmission. Through this call, CEPI aims to identify a lead and also collaborating partners to form one or two consortia. The consortia will carry out harmonised, reliable, and reproducible CHIM studies to the highest possible standards, focus on mucosal immunity, and support specific research projects to advance the development of vaccine candidates against betacoronaviruses under the functional activities described in Figure 1.

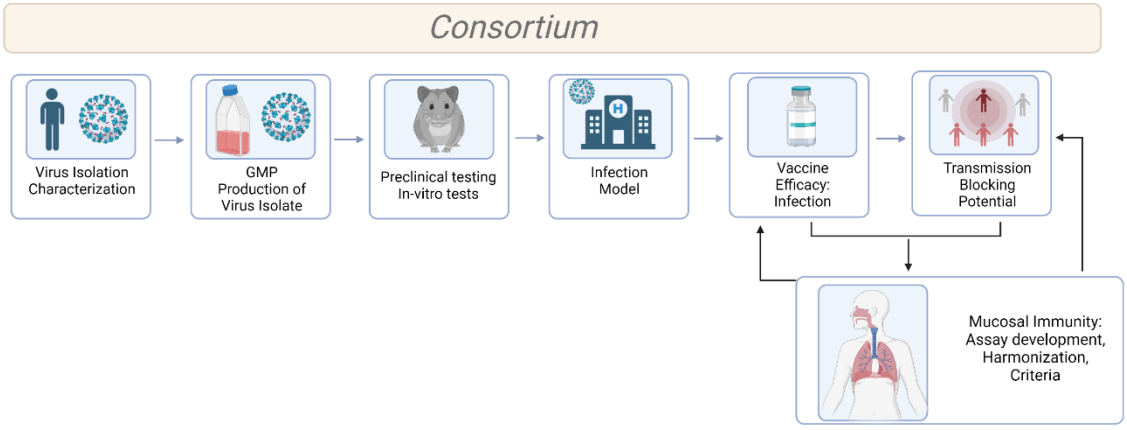

Figure 1. Outline of the betacoronavirus CHIM program to be covered by the consortium established through this CfP. *This program includes the following areas: (i) production and release of the challenge virus (including virus isolation & characterization, Good Manufacturing Practice (GMP)-like production of the virus isolate, pre-clinical/in vitro testing); (ii) development and characterisation of an infection model in non-naïve individuals and clinical characterisation; (iii) conduct of vaccine trial using CHIM; (iv) assessment of mucosal immunity and the transmission-blocking potential of vaccines; and (v) development of concepts for statistical analyses and systems vaccinology. The aim is to form a multi-country collaborative consortium to establish best practices for conducting CHIM and to evaluate vaccines against coronaviruses that target prevention of infection and/or transmission. (Figure created with Biorender)*

CEPI is seeking for applicants interested in forming an expert consortium to establish a CHIM platform to test novel mucosal vaccine candidates against betacoronaviruses. The lead partner will be responsible for overseeing all work packages within the programme.
We expect the consortium to carry out harmonised, reliable, and reproducible CHIM studies to the highest possible standards, to focus on mucosal immunity, and to support specific research projects to advance the development of vaccine candidates against beta-coronaviruses.

The expected outcome of the program is a multi-country network able to conduct CHIM studies with a high degree of harmonisation across study sites. The work packages cover harmonisation of procedures to release virus challenge stocks, conduct of CHIM and CHIM-based vaccine trials, evaluation of mucosal immunity, and integration of data sets. Guidance criteria should be developed for the assessment of mucosal immunity using harmonised standard operating procedures. Finally, the consortium will test novel vaccine candidates

and gain in-depth knowledge by comparing vaccine platforms, routes, adjuvants, and/or devices. With this program, we aim to improve the understanding of mucosal vaccine candidates in general and to facilitate strategies for vaccine-induced mucosal monitoring.

4. Eligibility criteria for partners

CEPI is looking to fund up to two consortia, preferably including partners from several countries and regions. There is no regional restriction. Applications can be submitted by individual partners willing to join a consortium or by an already formed consortium with a designated lead partner. It is CEPI's expectation that already-formed consortia have the expertise and capacity to deliver on all of the above-mentioned objectives and meet the eligibility criteria to operate accordingly. CEPI may ask individual applicants to form a consortium with other applicants. If a consortium does not include the strongest experts from the pool of applicants or lacks partners with required expertise, CEPI may suggest additional consortium partners. CEPI may supplement a consortium (that has applied for the programme) depending on the quality of the submissions of the individual partners. A willingness of the lead partner to accept new consortium partners is desirable.

Applicants must meet the eligibility criteria and demonstrate expertise in one or more of the research areas listed below. The eligibility criteria must be covered within the consortium:

- **Lead partner** has in-depth experience in preparing, conducting and investigating CHIM trials and/or vaccine trials in appropriate qualified facilities;
- **Lead partner** has a proven track record of managing complex clinical trial consortia and must be able to oversee and guide decision-making processes and provide regular reports to CEPI and its partners;
- **Clinical trial sites** are suitable and experienced for the conduct of CHIM studies and vaccine trials (BSL2/BSL3);
- **Biotech company/academic institution/university hospital** provide evidence for biobank expertise to provide clinical virus isolates;
- **Biotech company/academic institution/university hospital** have expertise in coronavirus life cycle, replication, and pathogenesis;
- **Biotech company/academic institution/university hospital** have the capacity and facility to grow, characterise, and produce virus challenge strain (GMP-like, BSL3);
- **Biotech company/academic institution/university hospital** provide evidence on their expertise in monitoring vaccine-induced mucosal immunity responses and experience in assay development and qualification;
- **Biotech company/academic institution/university hospital** have expertise in and capacity to measure viral transmission;
- **Academic partners** show substantial expertise in advanced biostatistical analyses of complex multi-dimensional data. A track record in machine-learning approaches is essential.

Successful proposals must meet the eligibility criteria stated above and clearly describe the capabilities and previous experiences of the applying entities. Applicants unable to demonstrate relevant experience will not be eligible for funding. Successful applicants are required to work closely together with CEPI and other external partners.

Under CEPI's Equitable Access provisions, procedures, reagents, and virus isolates developed and produced during this funding period will be made freely available to the research community.

CEPI's partner, the Animal Model Network, will support the program with regards to animal studies. CEPI's Centralised Laboratory Network (CLs) may support the consortium by evaluating the immunogenicity from vaccinated individuals. Contracts with sub-applicants covering a specific aspect will be supported by CEPI.

5. Applicant guidelines and review process

To respond to this CfP, please send a request with your intent to submit a proposal by email to BetaCoVCHIM.cfp@cepi.net mailbox by 20 August 2023. The BetaCoVCHIM submission template application will be provided along with instructions for submission to CEPI secure portal by unique customized link to ensure a secure submission process. We encourage applicants to submit their proposals well in advance of the deadline.

The submission should be uploaded in PDF format. No additional documentation other than those specified in the template should be submitted. An application from an individual partner or a consortium must state in the application form which of the eligibility criteria they and their partners intend to cover and describe their broad expertise in that area. Individual partners wishing to be integrated into a consortium must outline their area of expertise and declare their willingness to be included in a consortium.

For submissions to be accepted and registered, applications must fulfil the following:

- Meet requirements in section 4 (applicant eligibility criteria);
- Communication of information in English and documents in PDF format;
- Submit budget figures in US Dollars;
- Signed letters of support from all partners confirming their agreement to participate in the proposed projects;
- Applications should not exceed 20 pages (excluding references).

CfP submissions must include required evidence as indicated in the template, meet the timeline for completion, and contain sufficient detail to enable review of the proposed program. Any claims made within the proposal must be supported by evidence. Submissions that exceed the specified page limits outlined in the template or that fail to meet the above eligibility criteria will not be considered for further review.
Additional needs for technical support/clarification must be requested by email to:
BetaCoVCHIM.cfp@cepi.net
Timeline overview

- Call publication date: **20 June 2023***
- Deadline for requesting applications to BetaCoVCHIM@cepi.net mailbox: 1700 hrs CET, **20 Aug 2023***
- Applications submission deadline to CEPI secure portal: 1700hrs CET, **01 Sep 2023***
- Peer review and selection: **Q4 2023***
- Due diligence, contract signatures, project launch: **Q4 2023***
- Grant duration: 60 months

*NOTE: CEPI reserves the right to modify open CfP timelines in accordance with European Commission funding requirements for CfPs published on the EC Horizon Cascade Funding Calls.

The CEPI Secretariat will address any questions within the shortest possible timeframe. Any questions submitted, along with answers, will be anonymised and made public if relevant to the preparation of this application. Summary of frequently asked questions (FAQ) will be uploaded to the CEPI website.

All applications will be stored in a restricted access repository. Personal data included in proposals will be handled according to CEPI's Privacy Notice on www.cepi.net/terms/. CEPI will not cover any costs incurred for the development and submission of the application. Furthermore, CEPI will not provide funding retrospectively for activities carried out prior to an award.

6. Review criteria

Eligible submissions may be received from for-profit, non-for-profit organizations or consortia with the relevant expertise as outlined under the section 4. In case of a consortium, the lead applicant must represent a legal entity. To be considered for a contract award under this call, the consortium must cover all requirements. In the case of single applicants (for a consortia), the expertise in one specific field must be specified within the application.

Entities applying as consortia or single partner are required to use the application template and include the following:

1. **Comprehensive description of the institution applying as lead awardee,** including areas of expertise, departmental organisation (including organigram), scientific capabilities, international representation, and strategy. The lead partner should have extensive experience in conducting CHIM and/or vaccine trials in the last 5 years. The facility must fulfil all requirements for conducting betacoronavirus CHIM. Aspects that will be considered are technical competency/expertise of project staff, experience in clinical trials and CHIM, experience in regulatory interactions with competent authorities.
2. **Comprehensive description of an individual partner institution willing to join the consortium,** including areas of expertise, scientific capabilities, international representation and strategy. Expertise and capacities of partner entities, roles, and responsibilities within the consortium will be considered. Indicate willingness to collaborate with partners which CEPI considers appropriate to complement their expertise. The institution must fulfil all the requirements for the implementation of its specific field. Aspects that will be considered include the technical competence/expertise of the project staff, the soundness of the concept and the facilities and experience required depending on the area the partner wishes to cover.
3. **Details of experience with challenge virus production,** and manufacturing expertise at GMP quality standards. BSL2/BSL3 facilities are required. Aspects that will be considered are soundness of the concept to harmonise and accelerate the release of the virus challenge agent as well as willingness to share procedures, reagents and agents with research community.

4. **Experiences with CHIM and/or immune monitoring with a focus on mucosal immunity and transmission**. Include experiences in clinical human challenge infection models, and collaborating with multi-country consortia including partners from industry, academia and public health agencies, and dealing with regulatory authorities, health authorities and governments. Experiences with stakeholder and ethics committees.
5. **Experiences with vaccine trials** within the framework of CHIM and collaborating with multi-national consortia including partners from industry, academia and public health agencies, and dealing with regulatory authorities, health authorities and governments. Experiences with stakeholder and ethics committees will be considered.
6. **Scientific capacity**, including previous scientific contribution in the field of CHIM, virus challenge production, vaccine development, vaccine trials, mucosal immunity, and data science (statistical analysis and modelling). Track record in this field and the soundness of the concepts and the previous experience and track record will be considered.
7. **Logistical capacity,** including for example capacity to produce BSL3/GMP-like virus challenge stock or capacity to conduct CHIM in a BSL3 facility will be reviewed.
8. **Ensure compliance** of research projects with EU ethical standards and regulations and ensure engagement of Independent Ethics Advisory Board will be reviewed.
9. **Experienced relationship** with local ethics committee will be considered.

Applicants applying as a consortium should decide how many and which partners the consortium shall comprise of to achieve the goals in a most comprehensive, time efficient manner. Applicants have the right to include/contract 3rd party companies to fulfil the desired goals.

7. Award conditions

Before submitting the application, applicants should be aware that:

i) Each Awardee must adhere to CEPI's policies, which can be found on CEPI's website; and
ii) Any funding is dependent on signing an Award Agreement, which provides the terms and conditions under which the Award will be made, in line with CEPI's Third Party Code, which can be found on CEPI's website.

CEPI is committed to achieving equitable access to all CEPI-supported programmes including vaccines, platforms, data, results, and materials. Specifically, equitable access to vaccines in the context of an outbreak, epidemic or pandemic means that appropriate products are first available to populations when and where they are needed, regardless of ability to pay. To ensure that CEPI delivers on its commitment to equitable access, CEPI must include access considerations as a component of any agreement with an awardee. Applicants unable or unwilling to meet these requirements should not apply for this CfP.

8. Technical and administrative questions

Technical and administrative questions about this Call should be directed to the CHIM CEPI mailbox, **BetaCoVCHIM.cfp@cepi.net**.

Contract arrangements will be initiated along with the technical and financial due diligence and pursued to recommendations for funding to the Board by Q4 2023. For the candidates not proceeding to due diligence the CEPI Secretariat will seek to communicate as early as possible. The CEPI secretariat will publicly announce each award when the partnering

agreement has been signed. Applicants whose proposals do not advance to contract will be notified confidentially of the outcome of the process in a timely fashion.