CEPI

2.0 Programme Document

Unleashing the power of science to end pandemics

November 2021

Contents

Foreword from the CEO

Unleashing the power of science to end pandemics

The Coalition for Epidemic Preparedness Innovations (CEPI) was established after the West African Ebola epidemic to prevent the world from repeating its tragic failure to prepare for a foreseeable infectious disease. The world had begun work on a potential vaccine against the deadly Ebola virus, but complacency about the threat caused the vaccine to languish in the early stages of its development. Insufficient political and financial commitment meant that a highly effective, epidemic-stopping tool was not ready when it was needed most.

This fatal lack of preparedness allowed Ebola—whose threat was well characterised, and against which a nearly 100% effective vaccine was ultimately developed—to emerge in West Africa, spread to a number of countries around the world, and kill more than 11,000 people. This epidemic, as it turned out, was the harbinger of a vastly more dangerous threat to emerge just a few years later.

In the wake of the West African Ebola epidemic, it was clear the world needed a better way of speeding the development of vaccines against known threats and preparing for the rapid development of vaccines against the unknown threats that will surely emerge. Subsequent events have demonstrated that delivering at scale and ensuring access are as important as the raw speed needed to develop new vaccines against epidemic threats. During the response to COVID-19, unprecedented speed and scale was achieved, but access to life-saving vaccines for the poorest countries has lagged terribly. We clearly have much work ahead of us.

Research and development is critical to preventing pandemics, and much of this science can and must be done ahead of time. Since its launch, CEPI has rapidly come to play a critical role in promoting global health security and has demonstrated the power of science to drive epidemic and pandemic preparedness.

Over the past 5 years, CEPI has invested a total of US$2.312 billion - US$1.952 billion[1] into 35 candidate vaccines and US$360 million in other enabling science projects against known threats. Through these programs, CEPI has simultaneously advanced the development of 11 rapid response platforms to deploy against unknown threats, or Disease X. In its early years, CEPI allocated over US$140 million to support vaccine development against MERS, an investment that came to seem prescient when SARS-CoV-2, a related Betacoronavirus, emerged in 2020. These critical partnerships enabled CEPI to move with speed and agility to initiate COVID-19 vaccine development, most prominently on what became the Oxford/AstraZeneca vaccine. CEPI was also the first global investor in the Moderna vaccine, the first to recognise the dangers of vaccine nationalism, the first to establish a globally and technologically diverse portfolio of COVID-19 vaccines, and the first, and so far only, R&D funder to leverage its COVID-19 vaccine investments in the interest of equitable access.

The advances in vaccine technology and innovations in clinical development and regulatory science emerging from the COVID-19 pandemic have, for the first time in history, equipped humanity with the means to dramatically reduce or even eliminate the risk of future epidemics and pandemics.

CEPI's bold US$3.5 billion plan, in coordination with the efforts of national and regional partners, will harness these advances and unleash the power of science to prepare and protect the world against emerging epidemic threats. We know these threats are out there. We know how to stop them.

With the funding and political will to do so, we can end pandemics forever.

Richard Hatchett, CEO of CEPI

[1] Sum of signed up to amounts as of 30th September 2021

Executive Summary

In 2020 the world was brought to its knees by an invisible enemy, SARS-CoV-2, the virus causing COVID-19. Entire economies went into lockdown. Trillions of dollars were wiped from global markets, hundreds of millions of jobs lost, and decades of development gains swept away. By November 2021, more than 254 million people had been infected and over 5.1 million had died.

As the world struggled to come to grips with the unfolding pandemic, the scientific community rallied in response, displaying admirable solidarity as it threw the full might of human ingenuity against one of the greatest public health threats to confront the world in more than a century.

This pandemic acutely illuminated the glaring gaps in the global preparedness and response capabilities, which were known long before the emergence of COVID-19.

Following the devastating outbreaks of Ebola in Guinea, Liberia, and Sierra Leone in 2014-16, global health leaders mobilised to take concrete action against potential infectious threats. The World Health Organization (WHO) created an R&D Blueprint for Action to Prevent Epidemics[2], and the Global R&D Preparedness Monitoring Board[3] (GPMB) was established as an independent body. At the 2017 World Economic Forum[4],the governments of Norway, India, the Bill & Melinda Gates Foundation, the Wellcome Trust and the World Economic Forum agreed that a coordinated, international, and intergovernmental plan was urgently needed to develop and deploy new vaccines to protect against epidemics caused by emerging infectious diseases and enable access to these vaccines for people during outbreaks. Together they announced the creation of the Coalition for Epidemic Preparedness Innovations (CEPI).

CEPI – Scientific Promise, Speed, Scale, Access

For the first three years, CEPI prioritised high-risk pathogens in cases where developing a vaccine was deemed feasible and was forecasted to provide health, social and economic benefits for vulnerable populations, especially those living in low- and middle-income countries (LMICs). These high-priority pathogens included MERS, Nipah, Chikungunya, Lassa Fever, Rift Valley Fever and Disease X[5], in addition to finishing the job on developing vaccines against Ebola. CEPI's strategy (known as CEPI 1.0 Strategy) was to invest, coordinate and accelerate vaccine progression through clinical development towards delivery, making them accessible to all people in need.

When COVID-19 struck, CEPI was primed. The genetic sequence for SARS-CoV-2 was published on January 11, 2020. On January 23, when just 581 cases of the virus had been confirmed worldwide, CEPI launched its first three programmes to accelerate vaccine development against this novel pathogen.

CEPI could respond so quickly because of its significant prior investments in a number of vaccine rapid-response technologies capable of producing vaccines against unknown pathogens. CEPI had also identified coronaviruses as serious threats, allocating over US$140 million to the development of vaccines against MERS - a coronavirus similar to SARS-CoV-2. These investments and corresponding partnerships enabled CEPI to meet the COVID-19 challenge with agility, pivoting with its partners to establish the world's largest portfolio of COVID-19 vaccines, based on CEPI's core criteria of scientific promise and dedicated to achieving the three goals of speed, scale, and access. To date, CEPI has invested over US$1.6 billion in COVID-19 vaccine candidates.

[2] Who.int. 2016. An R&D Blueprint For Action To Prevent Epidemics Funding & Coordination Models For Preparedness And Response May 2016. [online] Available at: <https://www.who.int/blueprint/what/improving-coordination/workstream_5_document_on_financing.pdf?ua=1#:~:text=The%20WHO%20R%26D%20Blueprint%20for%20action%20to%20prevent%20epidemics%20addresses,therapeutics%20and%20diagnostics%20is%20costly.> [Accessed 13 October 2021].

[3] Gpmb.org. 2021. Home. [online] Available at: <https://www.gpmb.org/#tab=tab_1> [Accessed 13 October 2021].

[4] World Economic Forum. 2017. CEPI Initiative Aims to Prepare Vaccines to Speed Up Global Response to Epidemics. [online] Available at: <https://www.weforum.org/press/2017/01/cepi-initiative-aims-to-prepare-vaccines-to-speed-up-global-response-to-epidemics/> [Accessed 13 October 2021].

[5] "Disease X" represents the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease

Cognisant of vaccine scarcity, CEPI willingly took financial risks early in the pandemic and established contractual agreements that included equitable access commitments in an effort to offset the forces of vaccine nationalism and support global access. Working with Gavi, the Vaccine Alliance, and the WHO, CEPI conceived and helped establish COVAX, which, as of early November 2021, has delivered over 486 million vaccine doses to participating countries and economies—the largest and most complex rollout of vaccines in history. COVAX is central to the global vaccine response, especially for LMICs, within a dynamic context of active bilateral and regional procurement mechanisms. To date, more than 70% of vaccines shipped to LICs and more than 30% of vaccines shipped to LMICs have come through COVAX[6]. While this represents a vast improvement in access compared to past pandemics, CEPI recognises much work still needs to be done.

COVID-19 will not be the last major infectious disease outbreak. According to the WHO, 1,307 epidemic events occurred between 2011 and 2017[7]. Known diseases like cholera, plague and yellow fever have returned, while more recent ones such as SARS-CoV-1, MERS, Zika, and SARS-CoV-2, have emerged. CEPI's aim is to push the bounds of vaccine R&D and dramatically reduce, or even eliminate, the future risk of pandemics and epidemics, potentially averting millions of deaths and trillions of dollars in economic damage.

CEPI is now seeking to raise US$3.5 billion to implement its next five-year plan, which is presented in its CEPI 2022-2026 Strategy (hereafter known as the CEPI 2.0 Strategy) and supported by the CEPI US$3.5 billion Investment Case. Both documents are published on CEPI's website.

Find CEPI's 2022-2026 Strategy on our Governance website page

This CEPI 2.0 Programme Document describes how CEPI will implement its five-year plan to develop new vaccines which can be equitably deployed to protect against epidemics caused by emerging infectious diseases. CEPI offers a global focus, a proven track record, the agility to move quickly, and effective multisectoral partnerships. CEPI works to ensure the interests of LMICs are taken into account in global vaccine development and designs its portfolio to take into account applicability and use in low resource settings. CEPI leverages its unique connecting role—as a coalition of vaccine developers, manufacturers, sovereign governments, philanthropies, civil society and global health organisations—and extensive networks to pool and deploy resources in ways that nation states and regional bodies often cannot. CEPI has established strong working relationships with major national regulators on all continents and has built operational relationships with key international health bodies such as the WHO Pan American Health Organization (PAHO), Africa Centre for Disease Control (ACDC), Gavi and United Nations Children's Fund (UNICEF).

[6] Gavi.org. COVAX vaccine roll-out. [online] Available at: <https://www.gavi.org/covax-vaccine-roll-out> [Accessed 16 November 2021]

[7] Who.int. 218. Managing epidemics. Key facts about major deadly diseases. [online] Available at: <https://www.who.int/emergencies/diseases/managing-epidemics-interactive.pdf> [Accessed 13 October 2021].

CEPI 2.0 Strategy

The objectives of the CEPI 2.0 Strategy are threefold: to PREPARE for known epidemic and pandemic threats by developing vaccines and promising biologics against the most prominent threats, building on COVID-19 achievements and CEPI 1.0; to TRANSFORM the response to the next novel pathogenic threat by harnessing innovations in technology and systems to significantly reduce global vulnerability to threats of novel pathogen outbreaks; and to CONNECT emerging infectious disease (EID) stakeholders to enable rapid countermeasure development, effective response and equitable access for those in need.

A key aspiration is to develop a safe and effective vaccine in 100 days from the moment that a pathogen is sequenced and/or the need for a vaccine is recognised to initial availability for use. It took 326 days from the release of the SARS-CoV-2 genetic sequence to the first emergency authorisation by a stringent regulator of a COVID-19 vaccine. Had the same been achieved in 100 days, COVID-19 vaccines could have been available in late April 2020, rather than in early December 2020 and could have significantly averted the loss of life and destruction of livelihoods. By compressing vaccine development into just 100 days, the world could dramatically reduce the likelihood of future epidemics and pandemics becoming humanitarian catastrophes.

Strategic Objective PREPARE

In the next strategic period, CEPI will finish the work initiated during CEPI 1.0 to develop vaccine candidates and, where relevant, monoclonal antibodies against Lassa, MERS, Nipah, Rift Valley Fever and Chikungunya, and initiate vaccine and monoclonal antibody development programmes against other known threats. CEPI will work to end the acute phase of the COVID-19 pandemic and dramatically reduce the risk of future coronavirus pandemics by investing in the development of broadly protective SARS-CoV-2 and other *Betacoronavirus* vaccines.

Prior to the pandemic, CEPI had invested more than US$140 million in a portfolio of four MERS vaccine candidates, plus one pilot pathogen candidate from the rapid response platform programme. During the pandemic, CEPI invested close to US$1.6 billion to support the development of vaccines on a variety of technology platforms against COVID-19. Over the next strategic period, CEPI will make additional investments to develop vaccines that offer advantages over current vaccines (e.g., are easier to use or produce, are cheaper, etc.) and that provide enduring protection against SARS-CoV-2 variants. To help prepare the world for future coronavirus threats, CEPI has initiated a programme to develop vaccines that are broadly protective against the whole *Betacoronavirus* genus.

Strategic Objective TRANSFORM

Future outbreaks of novel pathogens are inevitable. Over 1.6 million yet-to-be-discovered viral species are estimated to exist in mammal and bird hosts. Diseases such as COVID-19 do not respect borders, so global scale readiness and geographical diversity in vaccine R&D and manufacturing—to enable a rapid and effective response—is a critical line of defence.

In the next strategic period, CEPI plans to harness innovations in vaccine development and manufacturing to dramatically reduce the global impact from unknown pathogens, by using vaccine prototypes and platform innovations to provide a substantial head-start in the battle against novel threats.

CEPI will develop a library of vaccine candidates against a range of virus families known to infect humans, with equitable access as the core mission. Just as prior research into MERS enabled the rapid advancement of vaccines against COVID-19, developing prototype vaccines against representative pathogens from virus families known to infect humans could greatly accelerate the development of vaccines against other emerging threats.

CEPI will also expand its reach, particularly working with LMICs, and increase its funding to transform outbreak preparedness and response through scaling enabling sciences to further accelerate vaccine development and deployment. These activities will rely on the existence of a strong, truly global coalition to push for collaboration and solutions that will enable a faster system-wide response.

As of November 2021, whilst billions of doses of COVID-19 vaccines have been administered worldwide, only 4.1% of people in low-income countries had received at least one vaccine dose[8]. The combination of limited global manufacturing capacity and vaccine nationalism has precipitated this situation and CEPI expanded its scope in 2020 to help support vaccine manufacturing so it was cheaper, faster, and closer to an outbreak. This included securing raw materials and investing in a globally distributed manufacturing capacity, as well as helping set up a Manufacturing Task Force as part of COVAX to develop mechanisms to address bottlenecks in production, including supply chain shortages.

Going forward CEPI will invest in the development of manufacturing innovations that have the potential to rapidly produce vaccines and other biologics at low cost and closer to where they are most needed. CEPI will especially focus on manufacturing innovations that can accelerate epidemic and pandemic responses or enable the scaling of production of vaccines and other biological countermeasures, particularly in LMIC settings.

Strategic Objective CONNECT

The Connect strategic objective is at the heart of how CEPI will operate, focusing on collaboration with others to achieve its mission, identifying the right opportunities, developing state-of-the-art products and delivering these into a well-functioning ecosystem.

The need for a more effective, robust global architecture to deal with emerging infectious diseases (EID) has been widely recognised, and countries are seeking to strengthen their own domestic and regional preparedness and response capabilities.

In the next strategic period, CEPI will connect stakeholders to enable rapid development of countermeasures, implement an effective response and enable equitable access to these countermeasures for those in need. To achieve this, CEPI will focus on securing financing for epidemic preparedness and response, improving coordination among key stakeholders to enable system readiness, and embedding equitable access principles as the foundation for any global EID response.

The lack of sustainable and accessible funding mechanisms has been a major barrier in the response to the COVID-19 pandemic. CEPI will be a strong advocate for new approaches to R&D financing as part of initiatives being proposed by the G20 and G7 governments for an additional US$75 billion, including instruments like the Global Health Threats Fund[9].

Improving coordination requires alignment and agreement by stakeholders on what the EID global architecture should look like and a common understanding of how it should sustainably function in the interpandemic period and in response mode. CEPI aims to work with partners to articulate the configuration of a "target ecosystem profile"—based on the learnings from Access to COVID-19 Tools Accelerator (ACT-A), COVAX, and recommendations from the Independent Panel for Pandemic Preparedness and Response (IPPR), the G7 Pandemic Preparedness Partnership (PPP), the G20 High Level Independent Panel (HLIP) and the Global Preparedness Monitoring Board (GPMB) in 2021. This profile should aim to include all EID activities,

[8] Ritchie, H., Mathieu, E., Rodés-Guirao, L., Appel, C., Giattino, C., Ortiz-Ospina, E., Hasell, J., Macdonald, B., Beltekian, D. and Roser, M., 2021. Coronavirus Pandemic (COVID-19). [online] Our World in Data. Available at: <https://ourworldindata.org/covid-vaccinations> [Accessed 8 November 2021].

[9] https://pandemic-financing.org/. 2021. A GLOBAL DEAL FOR OUR PANDEMIC AGE. [online] Available at: <https://www.g20.org/wp-content/uploads/2021/07/G20-HLIP-Report.pdf> [Accessed 13 October 2021].

from disease detection, through the development of vaccines and medical countermeasures—including enabling sciences, regulatory, manufacturing and financing and procurement — to distribution, administration, and monitoring of use. It should also help define the roles and responsibilities of different stakeholders in the ecosystem.

CEPI will also formalise and strengthen partnership agreements with organisations that can support the development of regional infrastructure and expertise in LMICs to undertake the clinical studies and enabling science activities required to advance vaccine development, support technology transfers, and develop national and regional manufacturing capacity to enable countries to take ownership of their national health security.

Inequitable access to vaccines during the COVID-19 response has caused unnecessary and preventable loss of life and prolonged the pandemic. CEPI aims to work closely with LMICs to develop interventions that will improve the health of their populations and enable access to vaccines and other biologic countermeasures (e.g., strengthening clinical trial networks; funding manufacturing innovations and developing partnerships to coordinate capacity; proactively engaging priority regional and country-level organisations for outbreak preparedness; etc.).

Typically, commercial market forces, principles of supply and demand, and investment decisions do not favor fragile economies. As witnessed throughout the COVID-19 response, these limitations create barriers for LMICs to access essential life-saving global goods. CEPI will seek to overcome such barriers by: promoting the adoption of a minimum set of equitable access requirements in new public funding and procurement arrangements by G20 and other significant government funders; building on the risk-sharing mechanisms developed by COVAX partners to reassure industry and enable faster procurement for LMICs in outbreak situations; and collaborating with LMICs to conduct demand assessments to target preparedness activities appropriately and quickly.

CEPI also proposes to strengthen engagement with industry by: continuing to invest in R&D in return for access to the technology for LMIC supply; and enabling technology transfer to broaden the supply chain, increasing the economic viability of CEPI-funded programmes, and driving manufacturing that improves health security.

CEPI has established itself as the global focal point for future epidemic and pandemic preparedness. This CEPI 2.0 Programme Document addresses the challenges of how the world can end the present pandemic and emerge stronger, more united, and better prepared for known and unknown future threats. Its ambition is achievable. CEPI is poised to enable the design of a global health security system for vaccines and related countermeasures that brings together the expertise of public and private sectors in a synergistic and cost-effective manner, while helping governments fulfil their domestic obligations and achieve their collective goals to mitigate the impact of future pandemics.

CEPI

2.0

VISION STATEMENT:

A world in which epidemics and pandemics are no longer a threat to humanity

MISSION STATEMENT:

Accelerate the development of vaccines and other biologic countermeasures against epidemic and pandemic threats so they can be accessible to all people in need

PREPARE

for known epidemic and pandemic threats

TRANSFORM

the response to the next novel threat

CONNECT

to enhance and expand global collaboration

100 day ASPIRATION

to develop a safe and effective vaccine in 100 days from the moment that a pathogen is sequenced and/or the need for a vaccine is recognised to initial availability for use.

Introduction

In the five years since its launch in 2017, CEPI has established itself as an essential component of the global health system. CEPI offers a globally coordinated approach to vaccine R&D, and an ability to deploy the benefits of its work to where it is needed most. CEPI links all its investments to a commitment to equitable access, particularly for LMICs.

Over the past five years, CEPI has invested US$2.312 billion[10] in 21 vaccine candidates against its priority pathogens, 14 COVID-19 vaccines, and other cross-cutting enabling projects to tackle diseases such as Lassa Fever, MERS, Rift Valley Fever, Ebola, Nipah, and Chikungunya. Many of these diseases are associated with heavy social and economic costs, especially in low resource settings. COVID-19, as the world has discovered, represents a truly catastrophic global threat.

Strong political will to invest in health security, a revolution in vaccinology, and a strong global desire to reduce pandemic risk form the backdrop to CEPI's new 5-year strategy, which focusses on strengthening the world's defences against COVID-19 and other coronaviruses and reducing the risk of future pandemics.

[10] Sum of signed up to amounts as of 30th September 2021

Table 1: Overview of CEPI's Achievements Over First 5-Year Strategic Period (CEPI 1.0)

Pathogen	CEPI's Achievements 2017-2021	
 Lassa	Advancement of the first ever Lassa virus vaccines into Phase 1 trials	21 vaccines candidates against five WHO R&D Blueprint-listed pathogens[11]
 MERS	Advancement of the first ever MERS vaccine into Phase 2	
 Nipah	Advancement of the first ever Nipah virus vaccines into Phase 1 trials	
 Rift Valley Fever	Two vaccine candidates undergoing preclinical studies	
 Chikungunya	First Phase 3 trial of a Chikungunya vaccine	
 Ebola	Supported clinical development contributing to two Ebola vaccines achieving licensure and WHO prequalification	
 COVID-19	Invested in 14 R&D COVID-19 vaccine candidates for global use, with 12 in clinical development, two reached emergency use listing and two terminated, with hundreds of millions of doses made available to COVAX through CEPI's investment	
 Disease X	Three rapid response platforms advanced through Phase 1, with potential to significantly improve speed of vaccine development against multiple pathogens	
 Cross-cutting activities	Includes an array of cross-cutting, enabling projects to develop standards and assays, preclinical models, the establishment of a centralised lab network to support COVID-19 vaccine studies, as well as preclinical studies, and the largest ever, multi-country Lassa epidemiology study - ENABLE Lassa programme	

As of November 2021

[11] Chikungunya was considered by WHO during its 2018 annual review but not shortlisted as a priority disease under the R&D Blueprint.

CEPI 2.0 Programme Document

CEPI's 2022-2026 Strategy (CEPI 2.0) was published in March 2021, modifying its mission and vision to accommodate the evolving infectious disease environment. Accompanying the CEPI 2.0 Strategy is CEPI's US$3.5 billion Investment Case, which identifies CEPI's unique capability to initiate ground-breaking R&D to prevent and contain infectious disease epidemics, with global equitable access at its core. Both documents are available on CEPI's website.

This CEPI 2.0 Programme Document presents the operational plan
to implement the CEPI 2.0 Strategy over the next strategic period[12].
It articulates the strategic objectives, targets, activities, partnership approach, and resourcing requirements for a budget of US$3.5 billion. It has been developed by assessing the implications and risks related to the new strategy and describes a series of ambitious programmes that aim to substantially reduce global epidemic and pandemic threats.

The CEPI 2.0 Programme Document builds on important lessons learned from the last five years, and emphasizes: 1) the need to remain flexible and able to respond to an unpredictable emerging infectious disease environment; 2) the critical importance of partnerships, collaboration and building consensus around a global pandemic architecture which can respond more effectively next time, and; 3) the imperative of equity—leaving no one behind—empowering all countries to be able to develop and deliver vaccines to protect everyone, everywhere.

CEPI has clearly demonstrated its effectiveness through its response to COVID-19. In the space of five months in 2020, CEPI created the world's largest portfolio of COVID-19 vaccines expertly selected to support accessibility[13] and conceived of a globally fair allocation system for COVID-19 vaccines: COVAX. The global R&D system, however, remains fragmented and the roles and responsibilities of key actors in this space must be clearly defined to maximise efficiency and ensure an effective and rapid response.

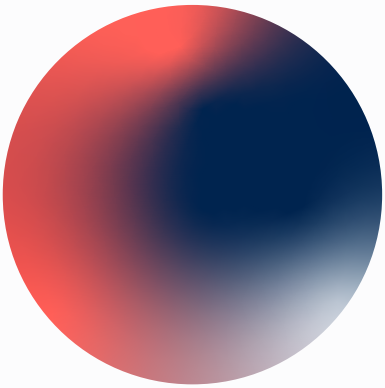
As the world begins to recover from COVID-19, it is hoped that a *post-pandemic consensus* will emerge in which governments and the private sector make sustainable commitments to global epidemic and pandemic preparedness. CEPI will work to transform the world's ability to respond
to new threats by investing in ground-breaking R&D, linking its investments with commitments to equitable access, and catalysing cooperation across a coalition of public and private sector partners.

With CEPI acting as an organising force for global R&D collaboration and scientific innovation, the world is within reach of a future in which epidemic and pandemic diseases no longer pose an existential threat to humanity.

[12] The Programme Document outlines CEPI's plan to deliver against CEPI 2022-2026 Strategy. Emerging future strategic areas for consideration e.g., therapeutics are not included in this document and the ask for US$3.5B financing. These emerging future strategic areas will be developed as needed in separate document(s).

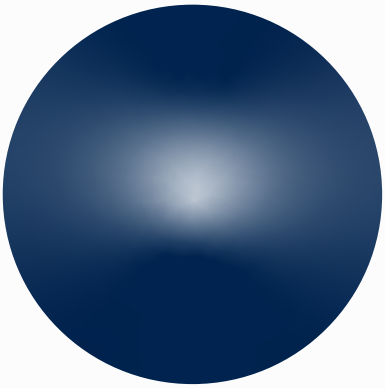
[13] As of 18 October 2021, CEPI has invested in the development of 14 COVID-19 candidates and secured right of first refusal to doses to the COVAX Facility. The COVAX Facility negotiates doses from COVAX R&D portfolio developers based on CEPI securing first right of refusal as well as through direct procurement, and from other developers. According to its latest Supply Forecast, in the most likely scenario and in the absence of urgent action by producers and high-coverage countries to prioritise COVAX, COVAX expects to have access to 1.425 billion doses of vaccine in 2021 and an additional 4.510 billion doses by end of 2022.

CEPI 2.0 Strategy



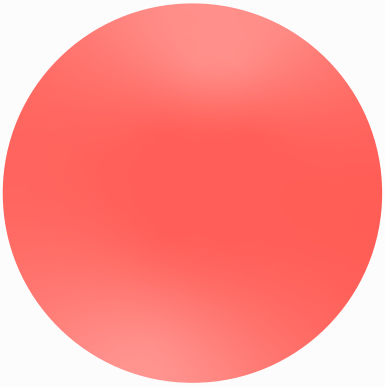
Vision

A world in which epidemics and pandemics are no longer a threat to humanity.



Mission

Accelerate the development of vaccines and other biologic countermeasures[14] against epidemic and pandemic threats so they can be accessible to all people in need.



Aspiration

To develop a safe and effective vaccine in 100 days from the moment that a pathogen is sequenced and/or the need for a vaccine is recognised to initial availability for use.

[14] Specifically, CEPI 2022-2026 includes additional biopharmaceutical approaches – such as monoclonal antibodies – because these are promising complementary approaches to vaccination for many outbreaks and will become increasingly important in the coming years.

Strategic Objectives

Prepare

for known epidemic and pandemic threats

Develop vaccines and promising biologics against the most prominent known threats, building on COVID-19 achievements and CEPI 1.0

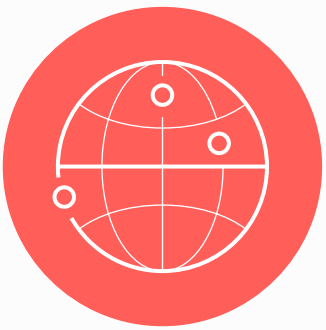
- End the acute phase of the COVID-19 pandemic
- Accelerate development of vaccines and other biologic countermeasures against known high-risk pathogens
- Reduce the risk of further coronavirus pandemics

Transform

the response to the next novel threat

Harness innovations in technology and systems to significantly reduce the global vulnerability to threats of novel pathogen outbreaks

- Use vaccine prototypes and platform innovations to give a head-start on novel threats
- Invest and scale critical enabling sciences to further accelerate vaccine development
- Transform vaccine manufacturing so it is cheaper, faster, and closer to an outbreak



Connect

to enhance and expand global collaboration

Connect EID stakeholders to enable rapid countermeasure development, effective response and equitable access for those in need

- Secure financing for epidemic preparedness and response
- Improve coordination among key stakeholders to enable system readiness
- Promote equitable access principles as the foundation of any effective response

The 100-Day Aspiration

The speed with which the world went from sequencing SARS-CoV-2 to vaccine availability was truly unprecedented. What usually takes a decade took 326 days. The world witnessed the start of a paradigm shift in vaccinology. In gauging how far this shift takes us, CEPI has set the audacious goal of establishing the capacity to develop a vaccine in just 100 days from the moment that a pathogen is sequenced and/or the need for a vaccine is recognised to initial availability for use.

These changes are not about reducing safety thresholds or forgoing the determination of efficacy. COVID-19 vaccine development has respected safety rules, and there is no reason to compromise them in the future. However, 326 days is not fast enough. COVID-19 has caused millions of deaths and trillions of dollars in economic damage. Reducing this development time to 100 days will significantly reduce the humanitarian and economic burden of future epidemics and, coupled with strengthened global biosurveillance for early detection and warning and the early use of nonpharmaceutical interventions to reduce disease transmission, could enable the world to prevent a pathogen with pandemic potential from becoming pandemic altogether.

The improvements already made in the vaccine development life cycle, and the ones to come, represent creative adaptations in every sphere: scientific and technical research, developmental work, manufacturing and regulation. The intense pressure and collaboration induced by a global pandemic has resulted in a transformation of how development contingencies and timelines are understood. There is a radically new understanding of the critical path for vaccine development.

CEPI was the first organisation to articulate the aspiration to develop vaccines that are available for use within 100 days of initiating development. This goal is central to the UK Government's proposed "100 Days Mission"—a roadmap for the rapid development and deployment of diagnostics, therapeutics, and vaccines in a future health crisis—that was embraced by the G7 Heads of State at the Carbis Bay Summit in June 2021. It also figures prominently in the Biden Administration's new pandemic preparedness plan ('*American Pandemic Preparedness: Transforming Our Capabilities*') and has been endorsed by the G20 Heads of State in their Leaders Communique from the Rome Summit.

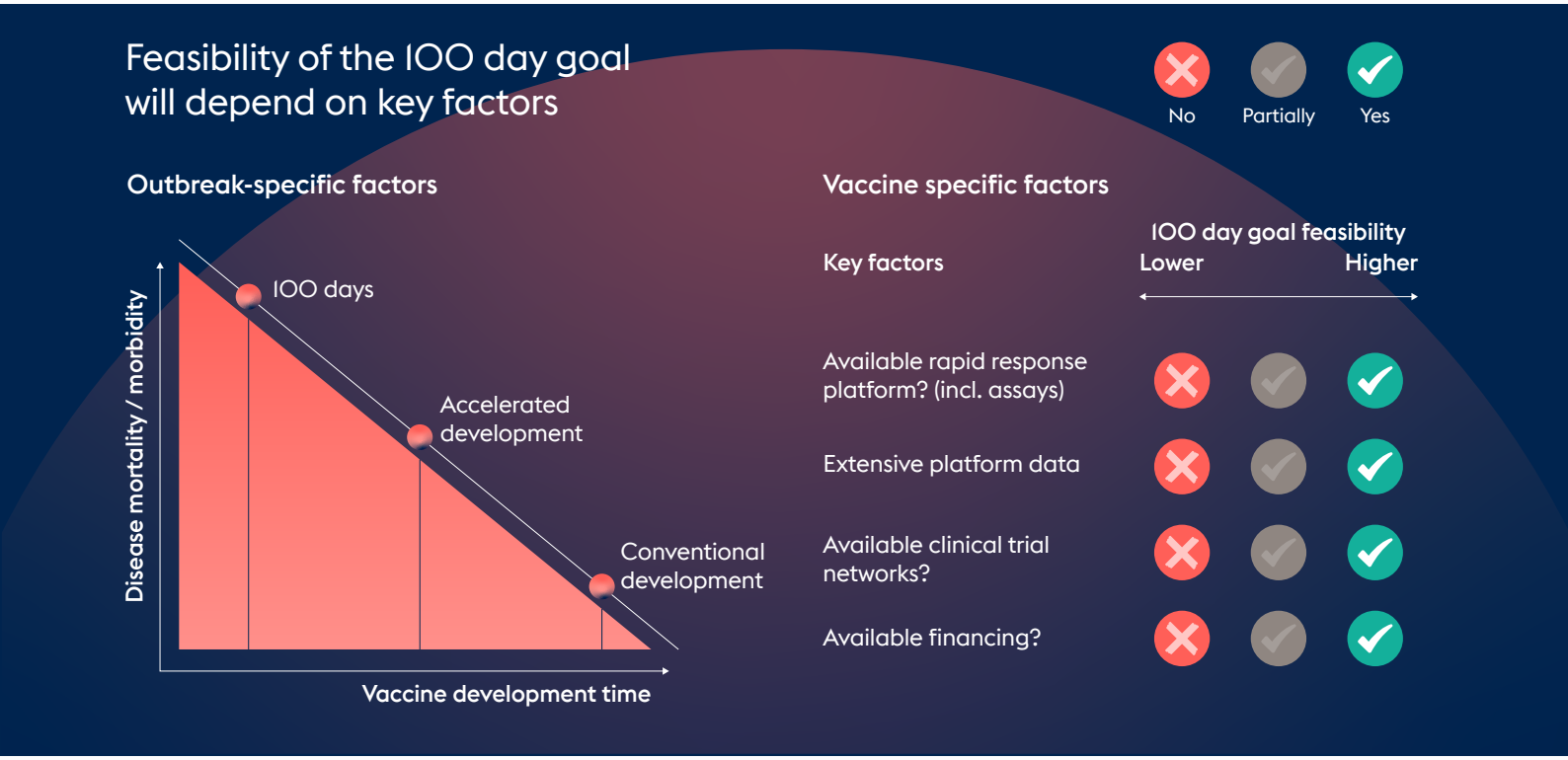
COVID-19 and vaccine development | What made the difference

The achievements of 2020 were not unlocked by a single moment of serendipity or the work of a single team. A number of breakthrough innovations developed both before and during the pandemic were critical enablers, as was the untiring and heroic work of stakeholders in vaccine development and deployment, and unequivocal backing from both public and private sources of finance. Underpinning these innovations, however, were a small number of core principles: those of prior knowledge available for deployment, multiple processes running wholly or partly in parallel, and significant collaboration between stakeholders globally.

In reviewing the events of 2020, it is clear that by combining the best practices from each of the successful efforts in COVID-19 vaccine development, an even faster process can be envisaged. Many of these improvements are contingent on work done in advance on an anticipatory and precautionary basis. Additional acceleration can be achieved in the application of preclinical models, clinical safety, dose-ranging and immunogenicity and Phase III efficacy trials. There is better understanding of how important it is to reserve sufficient manufacturing capacity and facilitate rapid and accurate technology and data transfer. The innovations in regulatory review undertaken in 2020 imply further time saving still. Taken as a whole, CEPI's analysis suggests these could reduce the time required for vaccine development by a further 15 to 25% (or by 50 days or more). Taken a step further, combining established best practice and known or highly probable innovations could reduce vaccine development time even further to a theoretical optimum of just 200 days.

Of course, no two outbreaks and no two pathogens are the same and so the optimal cycle time possible for each will be different. The most important factors driving this variation are set out in Figure 1. For example, whether a suitable response platform has been pre-identified, whether there is extensive platform data, whether there is availability of clinical trial networks and whether there is available financing all drive (or constrain) how fast the cycle can run.

Figure 1: Determinants of Optimal Cycle Time



The additional steps forward that can still be taken

To push this logic to its fullest extent—to accelerate vaccine development to just 100 days from the clock starting to first availability for use—requires breaking what has hitherto been full or partial firewalls between development, manufacturing, and intervention. These three sets of processes must be able to run in parallel.

By doing this, substantial further benefits can be unlocked in three ways. Significantly, the majority of these enabling steps will take place or relate to events before and after the 100 days which represent the response-specific critical path for any given vaccine. There are distinctions between (a) readiness, (b) response and (c) rollout and review.

Readiness relates to steps which have to be taken in advance of the triggering outbreak; response, to those which take place during the 100 days; and rollout and review, to those which must be ready to operate if the entire process is to be undertaken safely and effectively—and to be fit for purpose globally.

Readiness

CEPI's mapping of the initiatives that can deliver 100-day vaccine development has indicated five critical initiatives to allow us a rapid response to a new pathogen:

- Build a library of prototype vaccines
- Develop scalable plug-and-play vaccine and assay platforms for rapid adaptation

- Generate prototype safety and dosing evidence so that approvals are focused on the novel components for any vaccine (as is currently the case with seasonal influenza vaccine development)
- Maintain manufacturing capacity and clinical trial networks on standby for rapid activation
- Create cross-ecosystem partnerships and define governance framework for cooperation, financing and data sharing.

These initiatives all build further on the lessons learned in 2020. Critically, however, collaboration on an ecosystem scale will be necessary to have both the reach and resilience to capture what will otherwise remain theoretical benefits. Apart from anything else, this cooperation can help secure the manufacturing resources required to deliver a meaningful volume of finished vaccines appropriate to the nature and extent of a given outbreak.

Response

During the 100 days that represent a pathogen-specific critical path, it is necessary to characterise the outbreak for which the clock start has been triggered, develop a vaccine with performance and safety characteristics sufficient to justify emergency authorisation and produce sufficient quantities for human clinical trials and initial commercial use.

This sequence represents a significant number of decisions and activities, all of which can be accelerated to some extent by deep prior platform knowledge and expertise, prior agreement on protocols and the reservation of essential capacity to call upon at very short notice. Importantly, many of these steps can also take place in parallel. Every single step in the vaccine development cycle can and should be organised and sequenced to enable the fastest possible transit through the critical path—and minimise the time that it takes both by accelerating execution and handover and running key processes in advance and in parallel.

Rollout and Review

The development of vaccines for COVID-19 was characterised by an overlap between first emergency authorisation use and ongoing clinical interventional trials, together with a high level of cooperation and collaboration, often between competitors, to maximise vaccine manufacture and distribution. In order for 100-day turnaround to be feasible of any use, this rapid rollout in conjunction with the assembly and review of real-world evidence is essential. The two most important initiatives identified by CEPI for successful rollout and review to support the 100-day aspiration are:

- Confirming efficacy and safety in larger trials (providing readouts at some point after emergency use authorisation), and requiring investment to improve the pharmacovigilance infrastructure, especially in low and middle-income countries
- Enabling rapid global access by removing roadblocks for equitable vaccine roll-out (e.g., legislative, commercial / contractual).

Again, taking these steps will require effective coordination and collaboration across the entire vaccine development ecosystem.

Getting there | How CEPI can contribute

The 100-day aspiration speaks to CEPI's mission to reduce radically the impact of epidemics and pandemics and builds on the successes of the world's response to SARS-CoV-2.

By virtue of its positioning, CEPI can make substantial contributions to achieving this goal – whether in capturing and institutionalising the historic advances made in 2020, pushing forward the application of existing innovations or driving forward the critical preparations that will be instrumental to unlock the final acceleration of vaccine development.

Importantly, CEPI is in a unique position to bring together key stakeholders across industry, the regulatory landscape, academic and other public institutions, civil society organisations, and national governments to catalyse the critical conversations required for change.

Having collectively proven the old vaccine development model can be transcended, these trends should be pressed to their logical conclusion and a new paradigm evolved for the development of emergency medical countermeasures against pandemic threats. By doing so, the 100-day target can be brought within reach. The existential nature of pandemic threats demands nothing less.

Broader global partnerships and political support will be needed to further ensure that early signals, and subsequently new pathogen sequences are made available as quickly as possible. A mechanism for sufficient and tenable funding release is paramount to expedite vaccine development so that the 100-day aspiration also translates into rapid regulatory review and deployment of vaccine equitably where the potential benefits outweigh any risks.

The R&D focus areas and the CEPI 2.0 targets are complimentary. What is learned by pushing the envelope towards the 100-day aspiration will benefit our portfolio of vaccines targeting known pathogens (and vice versa) while these projects serve to maintain the 'readiness state' of research and manufacturing networks.

Prepare

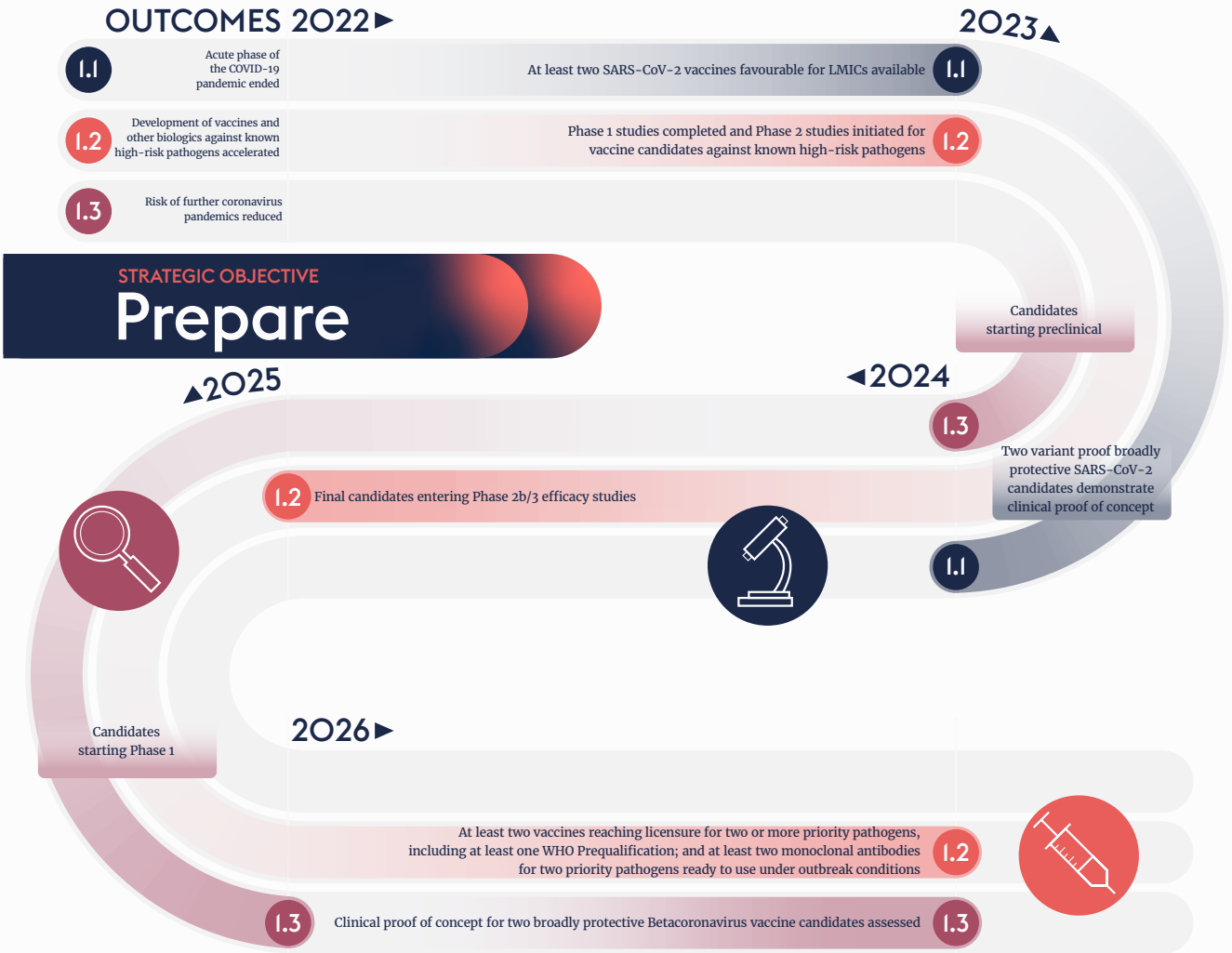
for known epidemic and pandemic threats

In the next strategic period, CEPI will contribute to ending the acute phase of the COVID-19 pandemic, finish the work initiated during CEPI 1.0 to develop vaccine candidates against known high-risk pathogens (originally selected from the WHO R&D Blueprint[15]), and dramatically reduce the pandemic risk presented by the uniquely dangerous family of Coronaviridae by investing in the development of broadly protective SARS-CoV-2 vaccines and Betacoronavirus vaccines.

Specifically, CEPI will:

- **End the acute phase of the COVID-19 pandemic**
- **Accelerate the development of vaccines and other biologic countermeasures against known high-risk pathogens**
- **Reduce the risk of further coronavirus pandemics**

Figure 2: Snapshot of PREPARE Roadmap to 2026



[15] Who.int. 2021. Background to the WHO R&D blueprint pathogens. [online] Available at: <https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/who-r-d-blueprint/background> [Accessed 13 October 2021].

End the acute phase of the COVID-19 pandemic

CEPI aims to substantially reduce, and in the long-term (beyond the CEPI 2.0 Strategy 5-year time frame), even eliminate the risk of epidemic and pandemic diseases. CEPI will continue to advance ongoing COVID-19 activities that were initiated and funded in alignment with current COVAX R&D and investment priorities.

CEPI has already made significant investments towards R&D and technology transfer for COVID-19 vaccines; but staying one step ahead of SARS-CoV-2 requires a multi-pronged scientific approach of genetic surveillance, continual laboratory testing of existing vaccines, and the development of new vaccine approaches, including work on variants and more broadly protective approaches to SARS-CoV-2. CEPI is doubling down across all these areas and has activated key elements of its plans now to mitigate the immediate threat posed by COVID-19.

CEPI will contribute to ending the acute phase of the COVID-19 pandemic by pursuing the following outputs:

- Advance an appropriate portfolio of COVID-19 vaccines
- Use portfolio of enabling science programmes

Advance an appropriate portfolio of COVID-19 vaccines

CEPI will continue its investments in first generation candidates that can offer doses to the COVAX Facility (the global procurement mechanism of the COVAX vaccines pillar of the Access to COVID-19 Tools Accelerator (ACT-A)). These investments will support evidence generation for policy decisions and optimising the use of available doses, and the availability of critical input supplies and manufacturing technology transfer.

In addition, CEPI is working on longer-term goals of funding next-generation approaches that offer advantages over the first generation and address the specific needs of a diverse range of populations and settings. CEPI will retain its position of right of first refusal to doses that will be offered through fair allocation mechanisms, such as the COVAX Facility.

To achieve this, CEPI will continue to:

- Fund late-stage clinical trials of promising vaccine candidates that can offer a right of first refusal to doses for the COVAX Facility
- Make additional investments in next-generation approaches offering advantages over the first generation, including vaccines against emerging variants of concern

While there exist multiple safe and effective vaccines against COVID-19, critical R&D questions remain which could expand access to vaccines by evaluating how they might work in at-risk populations, and whether some vaccines might be combined to boost efficacy or address supply disruptions.

To help advance our understanding of existing vaccines, and maximise access to them, CEPI is and will be funding a portfolio of clinical studies. These studies will:

- Explore vaccine safety and efficacy in HIV-positive, transplant, and other immunosuppressed patients
- Assess the use of mixed COVID-19 vaccine regimens for several vaccines in the COVAX portfolio
- Evaluate fractional dosing

Further, CEPI aims to rapidly expand access to the next wave of COVID-19 vaccines with a special emphasis on vaccines: with improved product characteristics or mode of actions preferred by LMICs, that target new variants of concern, and which optimise vaccine delivery in low resource settings, or cost-of-goods. This includes, for example, vaccine candidates that are single-dose, long-acting, and with thermostable characteristics.

Additionally, CEPI is also investing in more broadly protective vaccines against new emerging variants and variants of concern of the SARS-CoV-2 virus. In CEPI's Call for Proposal targeted at SARS-CoV-2 vaccine candidate development[16], CEPI cites a broadly protective SARS-CoV-2 vaccine with a minimal target product profile (TPP) to prevent disease caused by circulating SARS-CoV-2 variants of concern. This TPP could be expanded to also cite the prevention of disease against computationally predicted variants.

A provisional clinical proof of concept for broadly protective SARS-CoV-2 is defined as panel neutralization of all known variants of concern and neutralization of at least half of a panel of predicted variants of concern, and/or variants of interest[17]. CEPI will consider supporting further development and licensure of these vaccines on achieving clinical proof of concept if appropriate access provisions can be met.

Use portfolio of enabling science programmes

As SARS-CoV-2 continues to spread rapidly around the world, significant mutations in its genetic make-up have been observed which have impacted levels of viral transmissibility, the risk of re-infection, and vaccine immunity. It is critical that emerging new variants are rapidly characterised using high quality, standardised in-vitro assays and in-vivo models to determine the potential risk for mismatch with existing vaccines. Variant-specific antibody standard reagents and preclinical models are also needed. As new variants emerge, CEPI will continue to invest in several enabling science activities. These include:

- Expanding **the Agility programme** to assess the impact of emerging viral strains of SARS-CoV-2 on the effectiveness of COVID-19 vaccines. This programme is centred on a taskforce that includes the GISAID Initiative, Public Health England (PHE), and the National Institute for Biological Standards and Control (NIBSC). A first-of-its-kind collaboration, these organisations are working together to strengthen real-time global tracking and testing of SARS-CoV-2 variants, with special attention to location, spread and prevalence of variants and their defining mutations. Laboratory testing of the isolated variants in this programme assesses susceptibility or escape from neutralization by antibodies in convalescent sera taken from people after non-variant SARS-CoV-2 infection, the antigen upon which the current vaccines are based. If detected, evidence of reduced neutralization for new variants is quickly reported to stakeholders to raise concerns about specific circulating variants and possible decrease in vaccine effectiveness. To date, the Agility programme has assessed seven SARS-CoV-2 variants in standardised neutralization assays and all four variants of concern in *in-vivo* models at PHE and NIBSC. Highlights of *in vitro* and *in vivo* results are posted online as bi-weekly reports. Study protocols and detailed data reports are CEPI programme deliverables, and comparative data across variants will be compiled into peer-reviewed manuscripts for publication.
- Expanding the **CEPI Centralised Laboratory Network**, a global initiative to harmonise the assessment of COVID-19 vaccine candidates undergoing clinical studies and to evaluate subsets of clinical trial samples against priority variants of concern. This centralised laboratory network was established to minimise variation in assessment and allow for head-to-head comparisons between promising COVID-19 vaccine candidates. It is open to all COVID-19 vaccine candidates free-of-charge. The centralised laboratory network will expand to offer standardised testing capacities to vaccine developers for CEPI priority pathogens, as it currently does for SARS-CoV-2 vaccine developers. The network will also contribute to capacity strengthening through technology transfer of validated assays to laboratories located in different areas of the world, including in LMICs, and supporting labs to purchase instruments needed to perform quality testing at internationally acceptable standards.

[16] CEPI. 2021. Calls for Proposals – CEPI. [online] Available at: <https://cepi.net/get_involved/cfps/?learn-more-7099=3> [Accessed 13 October 2021].

[17] neutralization (>80% SC) of all known variants of concerns and neutralization (measurable / 4x Bkgr) of at least half of a panel of predicted variants of concerns, and/or variants of interest, using pseudo viruses

- Developing and expanding a network for developing **preclinical models** for SARS-CoV-2, including new variants.
- Supporting the International Vaccine Access Center (IVAC) in **tracking and evaluating the performance and safety of COVID-19 vaccines in clinical trials and real-world settings**, including against SARS-CoV-2 variants of concern.
- Facilitating the **epidemiological analysis and dissemination of genomic SARS-CoV-2 data** within the COVID-19 ecosystem and fostering relationships and collaborations with key external stakeholders in disease surveillance to inform vaccine development.
- Adapting **clinical development plans**, advising on required revisions for vaccines addressing variants of concern.
- Establishing a **network of systems immunology** partners to understand the breadth of response elicited by the vaccines.

Accelerate the development of vaccines and other biologic countermeasures against known high-risk pathogens

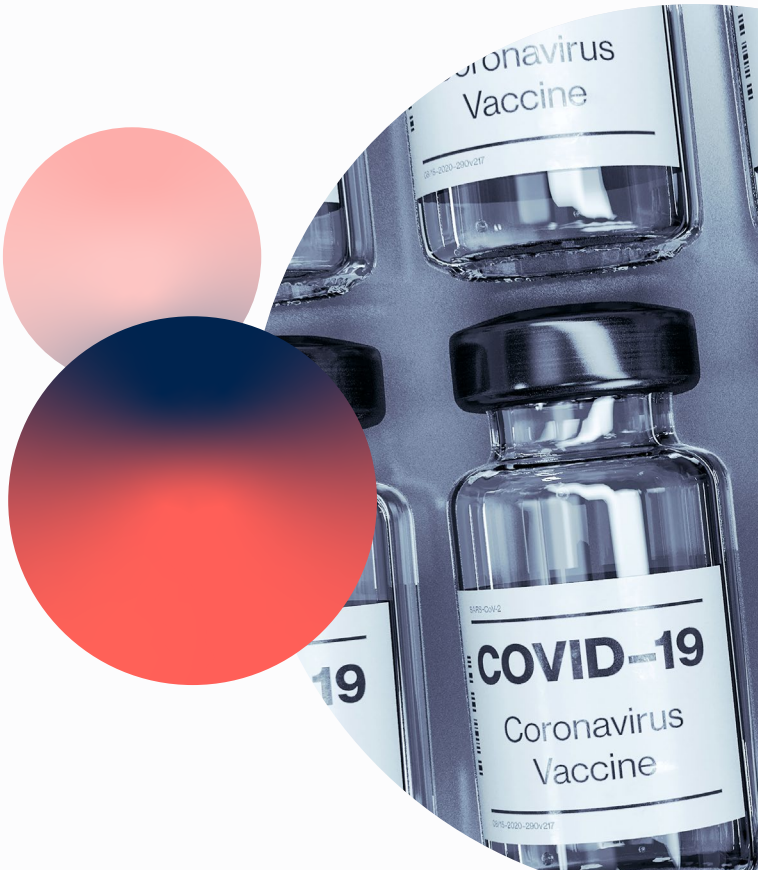
The principle of equitable access is at the forefront of CEPI's decision-making process, from the moment a vaccine candidate is assessed for funding to the moment it is procured and distributed by other organisations. CEPI is singularly focused on ensuring the vaccines and targeted biologic countermeasures whose development its supports are appropriate for use and easy to deliver in low-resource settings.

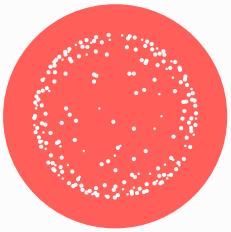
CEPI has been drawing on the WHO R&D Blueprint and other processes being developed to identify dangerous and epidemic-prone pathogens.
In the next strategic period, CEPI will continue vaccine development of priority pathogens beyond what could be achieved in the first strategic cycle (CEPI 1.0) and expand its support to late-stage (Phase 2b/3) development towards licensure for priority pathogens with a clear unmet need, where vaccines could have an impact. Diversity will be added to the existing portfolio by including some rapid response vaccine platform candidates which will also support CEPI's goals under the Transform strategic objective to further develop rapid response platforms.

The definition for priority pathogens differs between organisations and it is assumed that CEPI will retain the use of the WHO definition, namely: *"Diseases that pose the greatest public health risk due to their epidemic potential and/or whether there are no or insufficient countermeasures".*

Together with infectious disease experts, CEPI's Scientific Advisory Committee (SAC) and WHO, CEPI will continue to assess pathogens of concern and might consider adding up to two new priority pathogens to the portfolio.

In addition to investments in priority pathogen vaccine development, CEPI will also make some investments in countermeasures beyond vaccines, focusing on capabilities for prophylactic vaccine-like technologies (e.g., monoclonal antibodies) where this is beneficial for rapid response.





Advance vaccine candidates

Lassa

Lassa virus belongs to the Arenaviridae family and causes Lassa fever, also known as Lassa haemorrhagic fever (LHF). An estimated 100,000 to 300,000 infections of Lassa fever occur annually, with approximately 5,000 deaths. Surveillance for Lassa fever is not standardised; therefore, these estimates are crude[18]. While Lassa virus is typically spread when a person is exposed to the urine or faces of infected rodents—for example by handling contaminated food or household items, person-to-person transmission can also occur, primarily in health care or laboratory settings if appropriate infection prevention and control measures are not taken.

CEPI has invested in a portfolio of six Lassa vaccine candidates with development plans across a range of affected countries in West Africa, resulting in the advancement of the first-ever Lassa vaccines into Phase 1. At the moment, three candidates are in Phase 1a or 1b, with trials conducted in affected countries. CEPI has also invested in the largest epidemiology study of Lassa virus in West Africa, to expand epidemiological knowledge and understanding of disease transmission and prepare for a field efficacy study of the most promising vaccine(s).

In the next strategic period, CEPI will continue to advance several vaccine candidates through clinical studies towards the aim of licensure of a vaccine based on field efficacy trial for routine immunisation in affected regions.

To support this target, CEPI will continue to invest in supporting enabling science activities: advancing epidemiological understanding through the ENABLE Lassa research programme; strengthening clinical trial processes and networks; ensuring harmonisation of data across developers through established standards and assays; and enabling faster development by identifying and tackling regulatory bottlenecks.

Furthermore, the Lassa vaccines in CEPI's portfolio are based on innovative vaccine platforms which open opportunities for applying innovations in manufacturing and transfer of regional manufacturing capacity close to the outbreaks. To do so, and in line with the Connect strategic objective, CEPI will bring together relevant stakeholders to develop a roadmap for potential manufacturing technology transfer for when manufacturing capacity has been built.

[18] Cdc.gov. 2021. Lassa Fever | CDC. [online] Available at: <https://www.cdc.gov/vhf/lassa/index.html#:~:text=The%20illness%20was%20discovered%20in,therefore%2C%20these%20estimates%20are%20crude.> [Accessed 18 October 2021].

This target will require significant collaboration with ecosystem partners. Some partnerships, like the Enable consortium, have already begun. Other partnerships will be initiated, including:

- With national and regional regulatory authorities, to align on licensure requirements.
- Through CEPI's Memorandum of Understanding with the Africa CDC and with the Partnerships for African Vaccine Manufacturing (PAVM) initiative, to set targeted objectives relating to research, development and manufacturing for Lassa vaccines in CEPI's portfolio.

BOX 1:

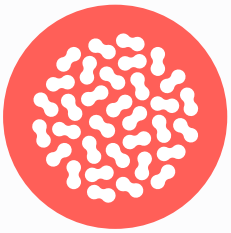
Equitable Access Case Study | How will CEPI's investment in Lassa Fever help Africa strengthen and sustain R&D and manufacturing capabilities and capacities?

There are no Lassa Fever vaccines currently approved for human use. Currently, CEPI has 6 Lassa vaccine candidates in its portfolio:

- Two of these Lassa vaccine candidates have entered clinical trials in LMICs.
- CEPI is also funding an epidemiological study across 5 West African countries (Benin, Guinea, Liberia, Nigeria, and Sierra Leone) to strengthen surveillance. In addition to identifying a baseline for measuring vaccine efficacy, data from these studies can facilitate the design and location of future Lassa vaccine trials and provide a framework for capacity strengthening for laboratory testing/ diagnostics and GCP for future vaccine trials.

Going forward, CEPI will:

- Continue to refresh the current portfolio, potentially down-selecting candidates where appropriate and including new candidates based on different platforms such as mRNA, or new antigen design approaches.
- Work with African CDC, WHO and partners towards supporting the nascent vaccine manufacturing industry in Africa.
- Facilitate technology transfer of the lead candidates to an African based vaccine manufacturer for late-stage manufacturing, including ready reserves to enable equitable access for LMICs.
- Co-ordinate dialogue between various stakeholders (AVAREF, Gavi, UNICEF, WHO, National regulatory authorities, manufacturers, etc.) to facilitate decision making on the vaccine deployment strategy (prophylactic versus outbreak response) and map out the regulatory licensure pathway.



Chikungunya

Chikungunya is an alphavirus that is transmitted by female Aedes mosquitoes and causes fever, severe joint pain, muscle pain, headache, nausea, fatigue and rash. The joint pain is often debilitating and can last for weeks to years. The disease shares some clinical signs with Dengue and Zika viruses and can be misdiagnosed in areas where they commonly occur. For several years now, the WHO has classed Chikungunya as a major public-health risk due to its high morbidity and has stated that further research and development is needed to mitigate the risk it poses. The societal cost of the 2013-2015 Chikungunya epidemic in the Americas is estimated to be around US$185 billion[19]. Yet, despite the large outbreaks and significant consequences of this disease, there is currently no specific antiviral drug treatment, nor any vaccines licensed for human use against this virus.

In January 2019, CEPI—with support from the European Union's Horizon 2020 programme—announced the launch of a US$48 million fund to develop safe and effective vaccines against Chikungunya (and Rift Valley fever) that will be accessible to vulnerable populations.

CEPI's portfolio of 3 Chikungunya vaccines has resulted in some success. Valneva announced positive Phase 3 results for its single-dose Chikungunya vaccine candidate in early August 2021[20]. It was also awarded FDA breakthrough designation, which intends to facilitate and expedite development and review of new drugs for serious or life-threatening conditions where preliminary clinical data demonstrates that the drug may have substantial improvement for at least one clinical endpoint over available therapies. CEPI also entered into a technology transfer agreement with a developing country vaccine manufacturer (DCVM), Instituto Butantan, to support the manufacturing of Valneva's Chikungunya vaccine candidate[21]. The International Vaccine Institute (IVI) and Bharat Biotech announced in August 2021 the launch of a global Chikungunya vaccine Phase 2/3 study trial in Costa Rica, supported through funding from CEPI and the Ind-CEPI mission of the Department of Biotechnology, India[22].

[19] Bloch, D., n.d. The Cost And Burden Of Chikungunya In The Americas. [online] EliScholar – A Digital Platform for Scholarly Publishing at Yale. Available at: <https://elischolar.library.yale.edu/ysphtdl/1022/> [Accessed 13 October 2021].

[20] GlobeNewswire News Room. 2021. Valneva Announces Positive Phase 3 Pivotal Results for its Single-Shot Chikungunya Vaccine Candidate. [online] Available at: <https://www.globenewswire.com/news-release/2021/08/05/2275182/0/en/Valneva-Announces-Positive-Phase-3-Pivotal-Results-for-its-Single-Shot-Chikungunya-Vaccine-Candidate.html> [Accessed 13 October 2021].

[21] Valneva.com. 2021. Valneva Awarded FDA Breakthrough Designation for its Single-Shot Chikungunya Vaccine Candidate – Valneva. [online] Available at: <https://valneva.com/press-release/valneva-awarded-fda-breakthrough-designation-for-its-single-shot-chikungunya-vaccine-candidate/> [Accessed 13 October 2021].

[22] CEPI. 2021. CEPI partners, IVI and BBIL, launch global Chikungunya vaccine Phase II/III trial in Costa Rica – CEPI. [online] Available at: <https://cepi.net/news_cepi/cepi-partners-ivi-and-bbil-launch-global-chikungunya-vaccine-phase-ii-iii-trial-in-costa-rica/> [Accessed 13 October 2021].

In the next strategic period, CEPI will offer additional funding to advance candidate vaccines towards licensure, through the alternative pathway and WHO prequalification with stockpile. Funding also includes enabling science activities, and mathematical modelling to inform demand and forecast needs, which is essential to the advancement of these vaccine candidates.
In addition, through the Connect strategic objective, CEPI will:

- Build the required partnerships to secure sustainable financing of Chikungunya vaccine development.
- Align regional stakeholders around manufacturing priorities.
- Work with countries and WHO to better understand local regulatory requirements and pathways towards pre-qualification of the vaccine(s).
- Work with downstream partners to initiate market shaping and define procurement and delivery plans.

BOX 2:

Equitable Access Case Study | How will CEPI's investment in Chikungunya help LMICs access vaccines?

In July 2019, CEPI entered into an agreement with Valneva to enable equitable access to Valneva's Chikungunya vaccine for LMICs in an end-to-end approach:

- Target product profile focused on LMICs including a plan for WHO prequalification and presentation in a low COGs manner
- Free virtual stockpile available before and after marketing approval of 200,000 doses
- Commitment to supply LMICs in event of an outbreak
- Technology transfer underway to Butantan in Brazil
- Commitment to increase manufacturing capacity in the event of an outbreak
- Commitment to equitable pricing principles.

Middle East Respiratory Syndrome (MERS)

Middle East Respiratory Syndrome (MERS) is a respiratory illness caused by a coronavirus called Middle East Respiratory Syndrome Coronavirus (MERS-CoV). This virus belongs to the same family of viruses that cause the common cold, severe acute respiratory syndrome (SARS), and COVID-19. MERS is a zoonotic disease, meaning it passes from animals to humans, and dromedary camels are thought to be the main source of infections in humans.

Prior to the pandemic, CEPI had invested more than US$140 million in a portfolio of four MERS vaccine candidates and related enabling science projects. These investments laid the groundwork to enable a rapid response to COVID-19 and enabled CEPI to pivot four projects, including the University of Oxford vaccine, to COVID-19 vaccine development.

In the next strategic period, CEPI will continue advancing candidate vaccines through Phase 2 clinical trials with the aim of potentially developing a ready reserve of vaccines which could be used to control regional outbreaks. As of today, an alternative pathway to licensure may be very challenging as the animal model for protection is a mouse model which may be difficult to equate to protection in humans. CEPI will explore how MERS vaccines—especially those developed on well-characterised platforms—could be used in ways to control an outbreak, while collecting the necessary data on effectiveness and safety.

It is expected that MERS R&D activities will merge into the wider coronavirus portfolio, which will include both vaccine candidates against COVID-19, and broadly protective Betacoronavirus vaccines. However, as broadly protective approaches may take several years, a MERS vaccine needs to be ready for use in an outbreak in the intervening time.

Nipah

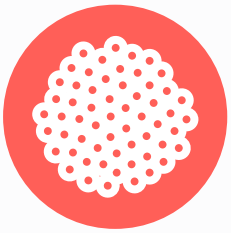
Nipah virus and the closely related Hendra virus have caused only a handful of outbreaks in Asia and Oceania, but the potential for much larger exposure is considerable, since more than 2 billion people live in parts of the world where Pteropus bats—the natural hosts of these viruses—are found.

Since the first known outbreak of Nipah in September 1998, Nipah has gradually expanded its range. The virus next emerged in Bangladesh and West Bengal in 2001, and over the past two decades has infected more than 300 people in these regions. In 2018, Nipah emerged on India's southwest coast, causing a small epidemic in the state of Kerala, more than 3,000km from Malaysia, where the first outbreak was reported 20 years previously.

So far, CEPI has committed over US$100 million to Nipah research and currently supports four early-stage vaccine candidates. One vaccine candidate, based on the licensed equine Hendra vaccine Equivac HeV, is now being tested in a Phase 1 clinical trial—the first time a vaccine developed to prevent Nipah virus infection has been studied in humans—and the other three are completing preclinical studies.

In the next strategic period, CEPI will continue to support vaccines in the pipeline towards licensure through alternative pathway with WHO prequalification, and with stockpile and will continue to engage with regulatory authorities in potential outbreak countries to evaluate the requirements to enable rapid deployment in the case of a future outbreak on the basis of animal and emerging clinical data.

In addition to developing a licensed vaccine against Nipah, CEPI's investments in this portfolio will contribute to its broader strategy by developing and validating the preclinical models that will ultimately support regulatory approval.



Rift Valley Fever

Rift Valley Fever (RVF) was first identified in 1931 during an investigation into an epidemic among sheep on a farm in the Rift Valley of Kenya. Multiple outbreaks have since been reported across the African continent and the Arabian Peninsula. To date, RVF has been found in over 30 countries. RVF mainly affects people living in pastoral communities in LMICs. The US CDC has classed Rift Valley Fever as a category A bioterrorism agent, given its potential to devastate large-scale agricultural economies and cause substantial social disruption.

CEPI currently has two Rift Valley Fever vaccine candidates in its portfolio. Both are undergoing preclinical studies.

In the next strategic period, CEPI will continue to advance a diversified vaccine portfolio through preclinical and clinical proof-of-concept with the aim to develop a vaccine through Phase 2 and ready reserve of vaccine which could be used in an emergency to control an outbreak.

BOX 3:

Equitable Access Case Study | How will CEPI's investment in RVF help with a One Health Approach?

Rift Valley Fever remains a priority pathogen for CEPI and projects will be progressed, science permitting, to clinical development. Rift Valley Fever also offers an opportunity to demonstrate in a tangible way the merits of the One Health approach, recently endorsed and communicated on November 3rd, 2021, at the G7 summit meeting.

- Human outbreaks predictably occur after an animal disease is detected and thus makes RVF a prime candidate for a One Health approach. CEPI intends to assess the viability of this approach through an investigation of the use of artificial intelligence, epidemiology and the coordinated use of vaccines for the affected human and animal populations.
- CEPI is currently invested in 2 live attenuated human vaccines and there is scope to further investigate the expansion of the portfolio with alternative technologies.
- CEPI's current plan for both existing projects and any new awardee is to carry out trials in endemic regions within LMICs.

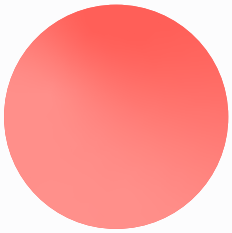
Ebola

Ebola virus disease (EVD), formerly known as Ebola haemorrhagic fever, is a rare but severe, often-fatal illness in humans. The virus is transmitted to people from wild animals and spreads through human-to-human transmission. The global need for CEPI was recognised after the devastating Ebola epidemic of 2014-16 in Guinea, Liberia, and Sierra Leone, which killed more than 11,000 people and had an economic and social burden of over US$53 billion.

To date, two Ebola vaccines have achieved licensure and WHO prequalification. CEPI has supported the generation of clinical trial data for both these vaccines, specifically generating data in HIV-infected people[23], infants and pregnant women. CEPI established an international consortium of global health partners to launch a second experimental Ebola vaccine as part of a clinical trial protocol (Ad26.ZEBOV/MVA-BN-Filo; Johnson and Johnson) in the Democratic Republic of Congo (DRC) in October 2019. The distribution of this vaccine candidate, in a clinical trial setting, allowed the collection of important data in a real-world setting on the administration of a vaccine that could be used to protect multiple vulnerable populations. To date, over 20,000 people have been vaccinated.

In the next strategic period, CEPI will finish the work started during CEPI 1.0 in relation to clinical trial data generation, continue to evaluate if additional filoviruses pose a threat, consider funding programmes, and evaluate the potential for improvements to manufacturing processes and delivery.

[23] In August 2021, the recruitment of the cohort 5 of the ACHIV-Ebola study started in Senegal and Burkina Faso. This arm of the Phase II randomised clinical trial is supported by CEPI as it will further inform on the safety and immunogenicity of the Ebola Virus Vaccine of Merck in HIV-Infected Adults and Adolescents. Primary outcomes include: (i) number of adverse events following V920 vaccination in HIV-infected adults and adolescents and (ii) immunogenicity of V920 via ZEBOV- specific antibody responses induced by V920 at D28.



New Priority Pathogens

In addition to the priority pathogens mentioned in this section, CEPI anticipates working on two new priority pathogens based on the emergence or re-emergence of pathogens with outbreak potential. As mentioned in the introduction of this section, together with infectious disease experts, CEPI's Scientific Advisory Committee (SAC) and WHO, CEPI will continue to assess pathogens of concern and might consider adding two new priority pathogens to the portfolio, looking at the WHO R&D Blueprint list of priority diseases and beyond.

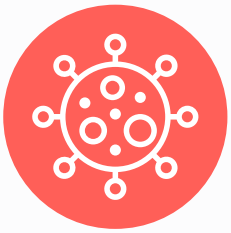
For CEPI 2.0, CEPI will develop its own methodological tool to assess the available scientific data on known viral pathogens with recognised epidemic or pandemic potential, to support decision making for CEPI's investment(s) in vaccines or other biologic countermeasure developments.

CEPI R&D will deliver a validated methodology with the goal to provide recommendations on which known pathogens to add, remove or maintain in CEPI's core portfolio, keeping in mind CEPI's focus on equitable access and the needs of LMICs. The need for a dedicated CEPI methodology will be supported by a landscaping analysis of pathogen prioritisation methodologies[24]. Note that the majority of the threats are viruses of zoonotic or environmental origin and, as such, these will continue to be CEPI's focus. We will continue to monitor emerging pathogens of outbreak, epidemic and pandemic potential and the need for vaccine development.

Advance monoclonal antibodies

In addition to vaccines, the availability of monoclonal antibodies for prophylactic use and post exposure treatment represents an important tool. These are closest to 'vaccine-like' approaches and offer rapid onset of protection in an explosive outbreak situation. They are readily amenable to a prototype pathogen approach, and can build on work in that area, such as AHEAD100. In theory, monoclonals could be available quickly in a crisis, with well-planned manufacturing. While technologies for their rapid adaption to viral mutations are continuing to mature, there is also a need for presentations/formulations that are easy to use in low-resource settings. Since they offer rapid protection against infection (vaccines take longer to provide protection since they must challenge the immune system), monoclonals may also be more appropriate for some diseases in which outbreaks are short-lived, and for which multiple-dose vaccine deployment is not feasible. CEPI will initiate the development of a monoclonal antibody programme against 4 priority pathogens. CEPI will focus on certain parameters – driving down costs and making these technologies accessible to all, with the aim of 2 priority pathogen prophylactic monoclonal antibodies ready for emergency use.

[24] A formal, documented, stepwise approach with an extensive set of parameters (inclusion/exclusion, selection criteria, ranking methodology, decision process, data availability, data imputation) will be developed to assess the knowns threats and rank them on a regular basis to inform decision making (TBD 1 or 2 times per business cycle).



Reduce the risk of further coronavirus pandemics

Advance broadly protective Betacoronavirus vaccine

Betacoronaviruses are types of coronavirus that have caused three major epidemics or pandemics in the 21st century: Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), which have been responsible for major epidemics in Asia and the Middle East in recent years, and also SARS-CoV-2, the virus responsible for the ongoing COVID-19 pandemic. CEPI has already begun the development of vaccines against SARS-CoV-2 variants of concern (see the section "*Advance an appropriate portfolio of COVID-19 vaccines*" for details), but additional approaches are needed to ensure that CEPI can stay one step ahead of the threat posed by these variants, other Betacoronaviruses, and potentially novel coronaviruses that have yet to emerge.

CEPI has therefore initiated a programme to develop vaccines against Betacoronaviruses with the ultimate objective of developing a vaccine that provides broad protection against the whole Betacoronavirus genus. Successful candidates in this programme would protect against SARS, MERS, SARS-CoV-2 and potential newly emerging threats from the broad animal reservoir of coronaviruses.

In CEPI's Call for Proposal targeted at broadly protective Betacoronavirus vaccine candidate development[25], CEPI cites active immunisation of at-risk individuals, to prevent disease and mortality caused by viruses belonging to the Betacoronavirus family[26]. A provisional clinical proof of concept is defined as the neutralization of all known Betacoronavirus human pathogens (with possible exception of the endemic Betacoronaviruses) and neutralization of half of a panel of zoonotic species within subgenera A, B, C, & D, with associated T-cell breadth where applicable[27].

Over the next strategic period, CEPI will build on the vaccine technologies validated in the COVID-19 response to develop a clinical proof of concept, building towards full scale development for two broadly protective Betacoronavirus vaccines. To do so, CEPI will invest towards assessing clinical proof of concept for broadly protective Betacoronavirus vaccines.

[25] CEPI. 2021. Calls for Proposals – CEPI. [online] Available at: <https://cepi.net/get_involved/cfps/?learn-more-7099=3> [Accessed 13 October 2021].

[26] Betacoronavirus family (proxy - robust [80%] neutralization against a panel of Betacoronaviuses)

[27] Neutralization [80% SC] of all known Betacoronavirus human pathogens (possible exception would be the endemic Betacoronaviruses) and neutralization of half of a panel of zoonotic species within subgenera A, B, C, & D; with associated T-cell breadth where applicable.

Performance management and monitoring of the Prepare strategic objective

CEPI will measure its performance towards the Prepare strategic objective using the following draft Key Performance Indicators (KPI) and Targets per Outcome (OC) and Output (OP), in the CEPI 2.0 strategic period 2022-2026:

- OC 1.1: Acute phase of the COVID-19 pandemic ended.
  KPI: Number of CEPI-funded SARS-CoV-2 licensed vaccines that are favourable for LMICs and available for use.
  Target: i) At least two SARS-CoV-2 vaccines favourable for LMICs available (by end 2022); ii) Two variant-proof broadly protective SARS-CoV-2 candidates demonstrate clinical proof of concept (by end 2023)
  - OP 1.1.1: Appropriate portfolio of COVID-19 vaccines advanced.
    KPI: Percent of interim milestones achieved for advancing CEPI-funded COVID-19 portfolio favourable for LMICs.
    Target: 100% of interim milestones achieved
  - OP 1.1.2: Portfolio of enabling science programmes used.
    KPI: Number of CEPI-funded enabling science programmes and innovative tools available for use in COVID-19 vaccine candidate development.
    Target: At least three
- OC 1.2: Development of vaccines and other biologic countermeasures against known high-risk pathogens accelerated.
  KPI: Number of CEPI-funded vaccine candidates and other biologic countermeasures for priority pathogens ready for use.
  Target: i) At least two vaccines reaching licensure for two or more priority pathogens, including at least one WHO Prequalification; ii) At least two monoclonal antibodies for two priority pathogens ready to use under outbreak conditions
  - OP 1.2.1: Vaccine candidates advanced.
    KPI: Number of CEPI-funded vaccine candidates advanced for each priority pathogen.
    Target: Two licensed vaccines, additional two vaccines in Phase 3 and four vaccines through Phase 2 with ready reserve of vaccine for use in an outbreak
  - OP 1.2.2: Monoclonal antibodies advanced.
    KPI: Number of CEPI-funded monoclonal antibodies advanced for each priority pathogen.
    Target: At least two monoclonal antibodies ready for use in an outbreak situation
- OC 1.3: Risk of further coronavirus pandemics reduced.
  KPI: Number of CEPI-funded broadly protective Betacoronavirus vaccines, favourable for LMICs, assessed for clinical proof of concept.
  Target: Two
  - OP 1.3.1: Broadly protective Betacoronavirus vaccine advanced.
    KPI: Number of CEPI-funded broadly protective Betacoronavirus vaccine candidates, favourable for LMICs, advancing through preclinical and Phase 1.
    Target: *Number of candidates per phase will be detailed in the interim milestones of this KPI in the Results Framework*

Transform
the response to the next novel threat

One hundred years ago the 'Spanish flu' killed an estimated 50 million people. Whilst the world's understanding of microbial threats has advanced immeasurably since then, increasing the ability to detect and react, worldwide populations remain vulnerable to sudden attacks by previously unknown pathogens, a threat WHO refers to as "Disease X". Designated as a priority under the WHO R&D Blueprint in 2018, Disease X "represent(s) the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease". COVID-19 represents the first occurrence of Disease X since this designation was established.

While the world battles to control COVID-19, a future Disease X is inevitable. The interconnected world has made humanity more vulnerable than ever to the rapid spread of new emerging infectious diseases. Rapid urbanisation, deforestation, intensive agriculture, livestock rearing practices, climate change and globalisation are increasing opportunities for animal-to-human contacts and for human-to-human transmission of disease on a global scale.

CEPI was able to respond swiftly to the COVID-19 pandemic because it had recognised the threat posed by Disease X. Through a call for proposals in 2018, CEPI had initiated a number of investments to achieve clinical validation of potential "rapid response platforms". Moreover, having already identified coronaviruses as serious threats, CEPI had allocated approximately US$140 million to the development of vaccines against MERS. Within a few weeks of the COVID-19 outbreak, all CEPI's rapid response vaccine development partners and most MERS vaccine development partners had pivoted to work on the new virus.

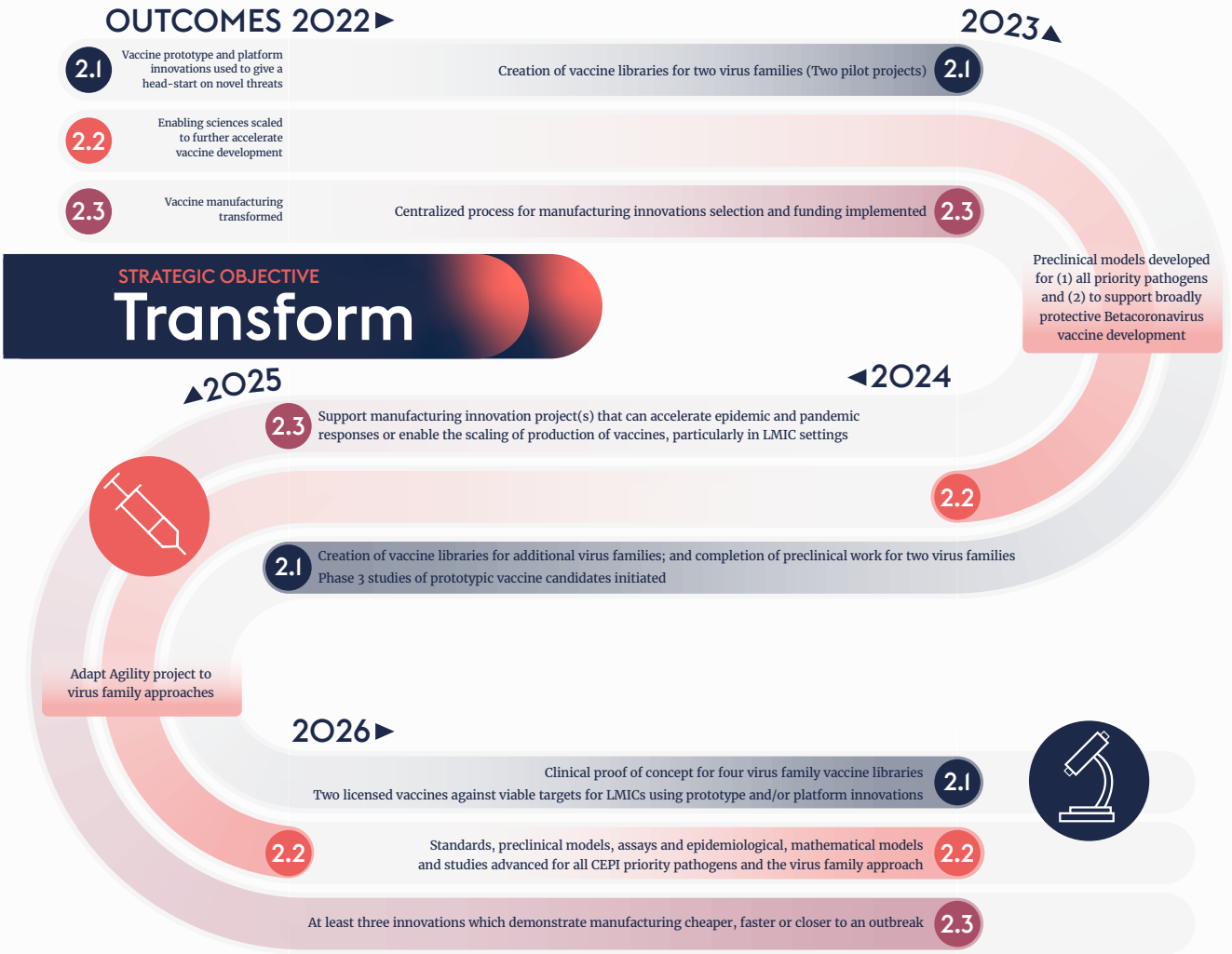
In many ways, it was fortunate that COVID-19 was a coronavirus and that scientists were already working on vaccines against MERS and SARS—pathogens from the same virus family as COVID-19—which gave CEPI a crucial head-start in initiating vaccine development. However, there are 27 viral families (>260 viruses) known to infect humans. The Global Virome Project estimates that 1.6 million viral species are yet-to-be-discovered in mammal and bird hosts—the most important reservoirs for viral zoonoses. Of those, an estimated 631,000 to 827,000 may have the capacity to jump species and cause diseases in humans. Compared with the more than 260 viruses known in humans, the unknown viruses represent 99·9% of potential zoonoses[28]. No one knows where, or when, or from which viral family the next Disease X will emerge, but the world needs to be ready to respond rapidly when it does.

Working towards the 100-day aspiration, CEPI will invest in preparedness to ensure a rapid response to novel emerging pathogens, and harness recent and future innovations in vaccine development and manufacturing to dramatically reduce vaccine development timelines. Specifically, CEPI will:

- Use **vaccine prototypes and platform innovations to give a head-start on novel threats**
- Invest and scale **critical enabling sciences to further accelerate** vaccine development
- Invest in **innovations so vaccine manufacturing is transformed to be cheaper, faster, and closer** to an outbreak

[28] Jonas, O. and Seifman, R., 2019. Do we need a Global Virome Project?. [online] Available at: <https://www.thelancet.com/action/showPdf?pii=S2214-109X%2819%2930335-3> [Accessed 15 November 2021].

Figure 3: Snapshot of TRANSFORM Roadmap to 2026



Use vaccine prototype and platform innovations to give a head-start on novel threats

In general product development terms, a prototype is defined as '*a first or preliminary version of a product from which other forms are developed*'. *CEPI intends to develop prototypic vaccines, which we conceive as 'a first or preliminary version of a vaccine against an exemplar virus from which other vaccines for related viruses can be rapidly developed*'.

CEPI will pursue two strategies to develop prototypic vaccines:

- Developing libraries of vaccine candidates against exemplar viruses from a range of virus families known to infect humans. These libraries are defined as 'collections of vaccine candidate constructs designed against viral pathogens, representative of families and their genus, that pose a significant risk to public health, that are themselves available for rapid response development and deployment and provide a template for vaccines against genetically related viruses'.

- Specifically leveraging developments in mRNA and other rapid response platforms, CEPI will seek to partner with major vaccine developers to develop prototypic vaccines for well-defined existing vaccine-preventable diseases. The aim will be to bring vaccines to the market using rapid response platforms and advance manufacturing capacity, particularly for LMICs. While this means that the prototype vaccine may not be indicated against pathogens of epidemic/pandemic potential, CEPI will instead seek to leverage indications that have existing correlates of protection and where cost-of-goods is expected to be low. Examples may include yellow fever, influenza and rabies. Ultimately, CEPI seeks to have an mRNA platform and/or other rapid response platform with a superior profile, accessible to LMICs, ready for use against future outbreaks.

Platforms such as mRNA have now been validated as rapid response platforms through the development of COVID-19 vaccines. Such technology platforms are likely to play a critical role moving forward in epidemic and pandemic preparedness, as they can be developed in significantly less time than more traditional approaches. However, many improvements need to be made to ensure mRNA and other platforms reach their full potential, for example, in terms of equitable access. It is therefore important to use the mRNA platform to develop vaccines for existing vaccine preventable diseases (e.g., yellow fever, influenza, rabies and Japanese encephalitis). This approach will help continue to gather platform data and at the same time build and sustain mRNA manufacturing and vaccine use. In the context of vaccine libraries, different families may need different approaches to be successful, so anticipating this work, CEPI may include other platforms as well to ensure candidates with the right immune profile.

Building a substantive pre-licensure platform safety database for a variety of vaccines is critical, so that when a new pandemic hits, the outstanding safety data needs will be focused on pathogen-specific questions. Careful characterisation of the immune response profile of a platform may aid in selecting the most appropriate platform for an emerging pathogen. Improving the manufacturing processes and supply chain infrastructure and investing in workforce development will be key to improving global preparedness.

In the next strategic period, CEPI proposes to do this by expanding its list of priority pathogens to further develop and characterise platforms, creating libraries of vaccine candidates, and working with vaccine development partners to develop prototype vaccines for existing vaccine preventable diseases on rapid response platforms (such as yellow fever, influenza, rabies and Japanese encephalitis).

BOX 4:
Innovative Rapid Response Platforms

The COVID-19 pandemic accelerated the development of vaccines on new and previously unvalidated platforms. These novel and now validated platforms will be powerful tools to react faster to future pandemics.

A vaccine platform is a technology, or group of technologies, that results in the presentation of an immunogen, or immunogens, to the human immune system for prophylaxis in a way that allows for "plug-and-play" swapping of immunogens. It is important to note that these technologies contain the modality by which an immunogen is delivered, the methods of its production, and associated data that support its characterisation and application. The platform is thus adaptable for the development and licensure of products against multiple pathogen targets. A rapid response platform has additional characteristics that accelerate development, particularly in construct generation, production and product release.

Over time, as master data files expand and regulatory agencies gain confidence in the platform, development requirements such as toxicity studies, clinical trial plans and process validations may be reduced, further accelerating development and licensure.

BOX 5:

Equitable Access Case Study | Why is CEPI investing in Vaccine Libraries?

Vaccine libraries are defined as collections of vaccines designed against viral pathogens, representative of virus families and their genus, which may pose a significant risk to public health.

CEPI is supporting the development of vaccine libraries through funding various projects, leveraging rapid response platform technologies, including mRNA, to achieve the following key objectives:

- Facilitate rapid response vaccine development and deployment for known/ future unknown pathogens of epidemic and pandemic threats, prioritising populations in need.
- Enable rapid and sustainable manufacturing, particularly within LMICs, to further enhance expertise and infrastructure in diverse geographies.
- Leverage "head start" from vaccine libraries to compress vaccine development timelines to achieve CEPI's 100-day aspiration.

Create libraries of vaccine candidates

It is not possible to develop vaccines against all potential viral threats, but vaccine candidate libraries can be produced for virus families which can be used or rapidly adapted if related viruses emerge.

Vaccine candidate libraries offer the potential to advance the starting point for rapid response vaccine development in a number of different ways. Against a matched or very closely related pathogen, the candidate vaccine may itself be useful, while against more distantly related viruses, it may serve as a template for rapid vaccine development, just as mRNA and ChAdOx MERS vaccines served as templates for the first vaccines developed against COVID-19. There are a number of virus databases that provide information on the genetic sequences and characteristics of known viruses. Databases such as ViPR, Viral Genomes-NCBI, Viral Zone and VirusDB will all be utilised as part of the computational immunogen design and in creating viral vaccine libraries[29].

Virus family prioritisation will support the investment case in vaccine libraries by ranking the viral families according to an explicit methodology and a set of selection criteria based on their potential risk to public health. Such prioritisation is thus distinct from, albeit related to, the WHO R&D Blueprint's current list of priority pathogens, whose selection is based exclusively on the public health risk presented by the specific individual pathogen. CEPI is currently actively developing a model and ranking system to prioritise and rank the family of viruses on their Disease X potential. Factors that will go into this ranking system include: transmission outbreak potential, zoonotic spill over potential, ability to mutate rapidly, mode of transmission and other important factors. To validate this ranking system, CEPI technical staff will work closely with its Scientific Advisory Committee, the WHO, and international experts in virological emergence potential. The final ranking will be used by CEPI to allocate resources and prioritise the development of vaccine candidate libraries for up to 10 virus families. Within the virus family, the library may consist of vaccine candidates against as many as 10-15 viruses, depending on the given family's phylogenetic diversity and including both human and zoonotic viruses that are deemed to present high risk. CEPI will enlist a panel of experts for each family of viruses to identify the appropriate viruses for the vaccine candidate library.

[29] CEPI will engage in creating libraries of vaccine candidates and does not intend to support the collection and management of actual virus isolates.

Developing CEPI's library of vaccine candidates for up to 10 virus families in the next 5 years will require substantial financial investment and commitment of human resources. To advance rapidly, this will need to be a shared global project with other partners, including NIH/NIAID, who will also work on vaccine prototypes for virus families. The strategic goal with coalition partners is to prepare for all high priority virus families with a high likelihood for a Disease X emergence. CEPI will not be directly collecting viruses, analysing new viruses or combining information from large virus collections, but will be working with international partners who are actively doing this. CEPI will be consolidating the information to create vaccine candidate libraries and hasten vaccine development for emerging or re-emerging pathogens with epidemic potential. Many institutions and funders will likely be working on this concept and CEPI expects to collaborate to ensure the efficient prioritisation and distribution of the work needed for this mammoth task. CEPI will invest in vaccine candidate libraries for virus families with the aim of demonstrating proof of concept for viruses with high probability of inducing outbreaks.

Given their closely related work in this area, collaboration and harmonisation with the US National Institute for Allergy and Infectious Diseases (NIAID) is a particularly high priority for CEPI. To this end, CEPI has initiated coordination meetings, with NIAID's Vaccine Research Center and extramural Division of Microbial and Infectious Diseases, to review the respective plans to address Disease X and the 100-day aspiration. Follow-up sub-group meetings are currently planned to address the science, vaccine development, regulatory approaches, clinical development and manufacturing and stockpiling of these vaccines. It is hoped that these meetings will result in coordinated funding opportunities, division of labour on viral pathogens, harmonisation of approaches, and sharing of data and other materials.

Novel digital technologies will be an integral part of the virus family vaccine candidate library development. The key to developing an effective vaccine is to target the antigen or set of antigens that produce an optimal immune response. Increasingly, such activities can be informed by simulations performed by computer modelling. CEPI will work with partners through a call for proposals to develop digital tools to design state-of-the-art vaccines. As a first step in this direction, CEPI is collaborating with the DeepMind's AlphaFold project in an effort to understand how digital technology could support library development.

CEPI expects to identify one or more developers that can use a validated mRNA platform to create the vaccine candidate libraries and good manufacturing practice (GMP) material for preclinical and clinical development of these vaccines. CEPI will explore other vaccine platforms on the assumption that the mRNA platform may be not be viable for all virus families. The ultimate goal is to develop a suite of rapid response vaccines to help tackle a future outbreak, which the regulatory authorities have agreed can be used as a "plug-and-play" platform.

CEPI is committed to providing the leadership to create the vaccine libraries, to design the vaccines, to support the preclinical and clinical development of these vaccines, to oversee the development of the master files and regulatory approval, to participate in simulation exercises of a potential Disease X emergence with Early Warning Surveillance partners, and to rapidly deploy CEPI resources from these libraries to work with international partners to contain a Disease X outbreak in line with CEPI's equitable access principles.

This approach has already paid off: vaccine research into HIV-1, RSV and MERS has advanced understanding of optimal antigen design and enabled the rapid advancement of vaccines against COVID-19. Developing vaccine candidate libraries of prototype pathogens in a virus family could greatly accelerate the development of vaccines against any newly emerging but related threats. CEPI's work on prototype pathogens is considered as a critical enabler of the 100-day aspiration.

Adapt vaccine platform technologies

Pathogens such as influenza and yellow fever have the potential to serve as prototype pathogens for further developing rapid response platforms such as mRNA, showing the value of these platforms beyond that already observed for SARS-CoV-2.

CEPI proposes a cost sharing initiative with a vaccine developer to develop at least two rapid response prototype vaccines for existing vaccine-preventable diseases. A priority consideration would be to make them accessible in outbreak situations through a fair allocation mechanism.

Pursuing viable targets will open avenues for cost sharing and support, bringing innovations to vaccines of interest for LMICs. CEPI intends to develop prototypic vaccines defined as 'a first or preliminary version of a vaccine from which other indications can be rapidly developed'.

CEPI will focus on these approaches in pursuit of the following objectives:

- **Generating data**: Developing prototype vaccines on platforms of interest will facilitate the generation of substantive safety, immunogenicity and efficacy data on the platform against an existing vaccine-preventable disease.
- **Improving the technology**: Developing new vaccines on promising platforms will iteratively improve the platforms and may lead to, e.g., improved thermostability, a more efficient manufacturing process, and lowered cost of goods – all of which will improve access.
- **Building platform manufacturing capacity**: Current manufacturing capacity for validated rapid response platforms is concentrated in Europe and North America. A more equitable distribution of such capacity will be essential to achieve better outcomes in future pandemics, particularly in terms of access. Developing vaccines for commercial markets on such platforms may enhance their sustainability.
- **Investing in speed**: By targeted investments in viruses such as influenza as a prototype pathogen and an example of a pathogen with need for rapid response, further work on speed of strain change could be practiced on an annual or semi-annual basis.

Scale enabling sciences to further accelerate vaccine development

Advance enabling science programmes

The success of CEPI supported vaccine development projects depends on its ability to develop a broader knowledge base of the pathogens themselves. To this purpose, CEPI has invested in a set of research activities needed to accelerate vaccine development, focusing on several enabling science projects related to the development of biological standards and assays, preclinical models, epidemiological studies, diagnostics, and clinical trial capacity.

In the next strategic period, CEPI will expand its reach and increase its funding to transform outbreak preparedness and response through scaling enabling sciences to accelerate vaccine development and deployment. These activities will rely on the existence of a strong, truly global coalition to push for collaboration and solutions that will enable a faster system-wide response (see the section "*Connect emerging infectious disease stakeholders to enable rapid countermeasure development, effective response and equitable access for those in need*" for additional details).

Specifically, CEPI will:

- Develop **biological standards and assays** for all priority pathogens, set up alliances, and establish platform development across immunology, assay technology and global serum collection networks.
- Develop **preclinical models** for all priority pathogens.
- Work closely with FIND to evaluate existing **diagnostic** assays and support assay development to ensure availability of high-quality assays for epidemiology studies, clinical trials, and vaccine deployment. Reagents and standards developed through the enabling science programmes for priority pathogens and Disease X will be made available to diagnostics developers.
- Conduct **epidemiological studies**: 1) assess burden of disease and circulating strains/variants of priority pathogens with epidemiological studies; 2) enhance disease monitoring /early warning and conduct threat assessments of pathogens of interest to inform CEPI's response and activate CEPI's assets; 3) inform pathogen prioritisation through a comprehensive epidemiological toolset, including impact modelling.
- Conduct **clinical trials**: 1) translate vaccine development strategies into scenario- and 'prototype'-pathogen-based clinical development plans; 2) develop and advance concept for vaccine pharmacovigilance strategies as well as risk management strategies for CEPI-supported developers and products; and 3) develop new concepts and scientific strategies for clinical research while exploring sustainable clinical capacity innovation and mechanisms.
- Invest in **digital technology** projects with the potential to accelerate vaccine R&D.

BOX 6:

CEPI's Enabling Sciences for Rapid Vaccine Development

Biological standards and assays

Development of biological standards and assays is important for evaluating vaccine-elicited immune responses and promoting standardisation, transparency, and comparability among the vaccine candidates. As more vaccines in the CEPI portfolio advance towards Phase I/II and, potentially, Phase III efficacy trials, access to common sets of reference standards will be crucial for the evaluation of the vaccine and the comparison of different vaccine candidates.

Preclinical models

Due to the nature of emerging infectious diseases, obtaining human efficacy data may prove challenging for the vaccines in CEPI's portfolio. Consequently, evidence of vaccine efficacy may need to rely, either in part or fully, on data from validated preclinical models acceptable to regulators. Therefore, CEPI is supporting animal model development/refinement and natural history studies that can serve as a basis for qualification of the model by regulatory agencies. It is aligning with the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) guidelines to accelerate the development of models and tools to avoid the use of animals where possible, reduce the number of animals used per experiment, minimise animal suffering, and improve welfare.

Diagnostics

Diagnostic tests can serve multiple functions, including epidemiological surveillance, diagnosis in efficacy trials, case detection, and outbreak response. CEPI focuses on supporting the development of diagnostic tests to prepare for Phase IIb/III clinical trials and identify cases of disease. Its efforts are in mapping the needs around the development of diagnostic tools, without which CEPI vaccine candidates cannot be advanced. CEPI has limited funding for diagnostics-related activities; therefore, the diagnostic work is mainly accomplished through establishing partnerships and collaboration with potential product development partners. Collaboration between FIND and CEPI will assure alignment of the development of virus family vaccines and corresponding diagnostic tools, and synergies on the 100-day aspiration.

Epidemiological studies

Epidemiological studies are essential to understand the incidence and prevalence of emerging infectious diseases, as well as their clinical characteristics and risk factors. These data are also essential to assess the feasibility of clinical field efficacy trials of promising vaccine candidates. To ensure the feasibility of efficacy trials and to support trial design, quality epidemiological data is needed. Epidemiological research can also help strengthen site and investigator capacity to conduct clinical trials. Therefore, CEPI is investing for epidemiological studies to collect data that can contribute to vaccine development in support of trial design, appropriate end points, and site capacity and support the development of a global rapid and nimble early warning system by key partners through active involvement/membership in relevant working groups.

Building clinical trial capacity

CEPI provides support with respect to the clinical development of vaccine, aiming to conduct clinical trials in affected endemic countries as early in the development process as possible. CEPI supports the identification of clinical trial sites covering target populations and engages in capacity strengthening. CEPI therefore supports scenario planning, clinical trial design, capacity strengthening, and other activities required for advanced-stage clinical trials to prove the vaccine candidate's efficacy against infection, disease, or both.

Novel digital technologies

Digital technologies and methodologies underpinned by artificial intelligence and machine learning have the potential to accelerate vaccine R&D and increase the probability of technical success. Particularly, this can include earlier detection of emergent diseases, accelerated and improved antigen design for Disease X and priority pathogens as well as accelerating development activities. A concrete example of such technology is the identification of the best possible targets for the development of a vaccine, crucial to counteract a virus's high infection rate (Choudhary et al., 2020). Since the outbreak of this first coronavirus, different AI-based approaches have been used to predict potential epitopes so as to design vaccines (Park et al., 2011; Yang and Leibowitz, 2015; Ton et al., 2020). Fast and Chen used MARIA (Chen et al., 2019) and NetMHCPan4 (Jurtz et al., 2017), two supervised neural network-driven tools, to discover potential T-cell epitopes for SARS-CoV-2 close to the 2019-nCoV spike receptor-binding domain (RBD) (Fast and Chen, 2020). CEPI will consider investing in technology projects with the potential to decrease R&D timelines.

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BOX 7:

Equitable Access Case Study | How is CEPI's investment in the Centralised Laboratory Network strengthening LMICs and enabling head-to-head comparisons of vaccine candidates?

CEPI's Centralised Laboratory Network (CLN) first opened to all COVID-19 vaccine developers—both CEPI-funded and non-CEPI-funded—free of charge in October 2020, for the analysis of vaccine clinical trial samples, up to Phase III studies.

- Through centralising the analysis to a group of selected laboratories worldwide, samples obtained from trials of COVID-19 vaccine candidates are instead tested by the same group of laboratories using the same methods and key reagents (i.e., substances used to carry out a laboratory test), removing much of the inter-laboratory variability and allowing for head-to-head comparisons of multiple vaccine candidates.
- To date (Nov 2021) CEPI has committed ~ US$18M, 45 COVID-19 vaccine developers have now used the service, with more than 15,000 clinical trial samples submitted for testing.
- Next step is to expand global footprint of the Network including labs in Africa, South America and Oceania; Strengthening the CLN network will not only expand the geographical footprint but also focus on efforts such as - capacity strengthening in LMICs, support all COVID-19 vaccine developers with better outreach to LMICs, standardise and harmonise the immunological measurements, support CEPI portfolio decisions and development of other CEPI priority pathogens.

Transform vaccine manufacturing so it is cheaper, faster, and closer to an outbreak

Advance manufacturing innovations

One positive outcome of the COVID-19 pandemic has been the development, manufacture, and deployment of safe and effective vaccines at unprecedented speed and scale. However, whilst billions of doses of COVID-19 vaccine have been administered worldwide—an outcome that would previously have taken years—far more doses are required as soon as possible, and they need to be produced rapidly, to enable equitable access. As of November 2021, only 4.1% of people in low-income countries had received at least one dose[30].

This situation was predictable. In early 2020, many called for developing additional, globally distributed manufacturing capacity, including in LMICs, to make more vaccines, remove reliance on just a few countries and mitigate the shortage in supply that has exacerbated the inequities. However, there was no entity responsible for organising or funding manufacturing, especially at-risk manufacturing. Global supply relied on manufacturing facilities in a handful of countries which prioritised protecting their own domestic populations. This resulted in a global shortfall in vaccine doses as well as profound inequities in access.

Looking forward, countries and regions with limited to no vaccine manufacturing capacity are aspiring to address their public health vulnerability and take control of their national or regional health security, through establishing local vaccine manufacturing capability. A challenge will be to build quality, sustainable manufacturing capacity, as well as develop viable business models to sustain such capacity during the interpandemic period.

CEPI, out of necessity, expanded its scope in 2020 to include securing raw materials and manufacturing capacity, as well as helping to set up a Manufacturing Task Force under the COVAX umbrella, to address supply chain shortages and identify mechanisms that could result in rapidly producing more vaccine doses.

In the next strategic period, CEPI will invest in the development of manufacturing innovations that have the potential to produce vaccines and other biologics cheaper, faster and closer to an outbreak. Additionally, geographically diversified global manufacturing capability is also an important part of the Connect objective in CEPI's 2.0 strategy.

CEPI has initiated a US$60 million programme with Wellcome Leap focused on mRNA technology to increase exponentially the number of biologic products that can be designed, developed, and produced every year, reducing their costs and increasing equitable access. CEPI aims to create a self-sustaining network of manufacturing facilities providing globally distributed, state-of-the-art surge capacity to meet future pandemic needs. CEPI will also complete the evaluation of the RNA printer technology (see Box 8); apply other mobile, small footprint manufacturing technology to CEPI-funded priority pathogen vaccines that are deemed to have a high probability of success; and invest in additional manufacturing innovations that can accelerate epidemic and pandemic responses or scale manufacturing, particularly in LMIC settings.

BOX 8:
Example of Applying Innovative Manufacturing Technology

One example in this area is CEPI's partnership with CureVac for the ongoing development of The RNA PrinterTM prototype—a transportable, down-scaled, automated messenger RNA (mRNA) printing facility. This innovative platform will provide a rapid supply of lipid-nanoparticle (LNP)-formulated mRNA vaccine candidates that can target known pathogens (including Lassa Fever, Yellow Fever, and Rabies) and prepare for rapid response to new and previously unknown pathogens (referred to by WHO as "Disease X"). The RNA Printer™ is capable of producing several grams of LNP-formulated mRNA (enough to produce more than a hundred thousand doses), within just a few weeks. This platform can also produce mRNA vaccine candidates against multiple pathogens using the same technology, saving time and reducing costs compared with other vaccine platforms.

[30] Ritchie, H., Mathieu, E., Rodés-Guirao, L., Appel, C., Giattino, C., Ortiz-Ospina, E., Hasell, J., Macdonald, B., Beltekian, D. and Roser, M., 2021. Coronavirus Pandemic (COVID-19). [online] Our World in Data. Available at: <https://ourworldindata.org/covid-vaccinations> [Accessed 08 November 2021].

Performance management and monitoring of the Transform strategic objective

CEPI will measure its performance towards the Prepare strategic objective using the following draft Key Performance Indicators (KPI) and Targets per Outcome (OC) and Output (OP), in the CEPI 2.0 strategic period 2022-2026:

- OC 2.1: Vaccine prototype and platform innovations used to give a head-start on novel threats.
  KPI: Number of CEPI-funded innovations that can be rapidly adapted against unknown pathogens.
  Target: i) Two licensed vaccines against viable targets for LMICs using prototype and/or platform innovations; ii) Clinical proof of concept for four virus family vaccine libraries
  - OP 2.1.1: Libraries of vaccine candidates created.
    KPI: Number of virus family vaccine libraries which have demonstrated proof of concept for viruses with high probability of inducing outbreaks.
    Target: Clinical proof of concept for four virus family vaccine libraries and preclinical proof of concept for additional six virus family vaccine libraries
  - OP 2.1.2: Vaccine platform technologies adapted.
    KPI: Number of prototype vaccines for existing vaccine preventable diseases (with prevalence in LMICs) using rapid response vaccine platforms.
    Target: Two licensed vaccines against viable targets for LMICs using prototype and/or platform innovations
- OC 2.2: Enabling sciences scaled to further accelerate vaccine development.
  KPI: Enabling science programmes and innovative tools actively used by CEPI-funded developers to further accelerate vaccine development.
  Target: Three or more of the enabling science tools developed through CEPI funding used by one or more of CEPI-funded vaccine developers
  - OP 2.2.1: Enabling science programmes advanced.
    KPI: Number of enabling science programmes and innovative tools to accelerate vaccine development advanced.
    Target: Standards, preclinical models, assays and epidemiological, mathematical models and studies advanced for all CEPI priority pathogens and the virus family approach
- OC 2.3: Vaccine manufacturing transformed.
  KPI: Number of new technologies demonstrating manufacturing cheaper, faster or closer to an outbreak.
  Target: At least three innovations which demonstrate manufacturing cheaper, faster or closer to an outbreak
  - OP 2.3.1: Manufacturing innovations advanced.
    KPI: Number of manufacturing innovations advanced.
    Target: ~5 manufacturing innovation projects advanced

Connect

to enhance and expand global collaboration

The global response to COVID-19 has exposed the fragmented and uncoordinated nature of the current preparedness and response architecture for EIDs of outbreak, epidemic and pandemic potential. Lack of coordination and clarity of roles[31] ; absence of established surge financing mechanisms for R&D, at-risk manufacturing and procurement; and lack of mechanisms to enable equitable access to vaccines, diagnostics, therapeutics and critical equipment, have all slowed the response.

In an effort to bridge these gaps, ACT-A and COVAX were established, and unique technical and logistical multilateral collaborations were set up. However, the need for a more effective, robust and coordinated global preparedness architecture is widely recognised, and countries are now seeking to strengthen their domestic and regional preparedness and response capabilities. An important aspect of the CEPI 2.0 Strategy is to enable connecting and leveraging such national, regional and global capabilities for R&D and manufacturing of biological countermeasures to meet the needs of all countries effectively, especially in LMICs.

To facilitate coordination and clarity of roles and responsibilities, CEPI will work with partners to align on what a more efficient and robust preparedness and response ecosystem should look like. CEPI has termed this vision a "**target ecosystem profile**". It will be based on learnings from the Access to COVID-19 Tools Accelerator (ACT-A), COVAX, and recommendations from the Independent Panel for Pandemic Preparedness and Response (IPPR), the G7 Pandemic Preparedness Partnership (PPP), the G20 High Level Independent Panel (HLIP) and the Global Preparedness Monitoring Board (GPMB) in 2021. This profile should aim to include all EID activities, from disease detection, through the development of vaccines and medical countermeasures—including enabling sciences, regulatory, manufacturing and financing and procurement — to distribution, administration, and monitoring of use. Achieving broad agreement about the configuration of such a "**target ecosystem profile**" would be a significant milestone and allow for improved coordination in response to future threats.

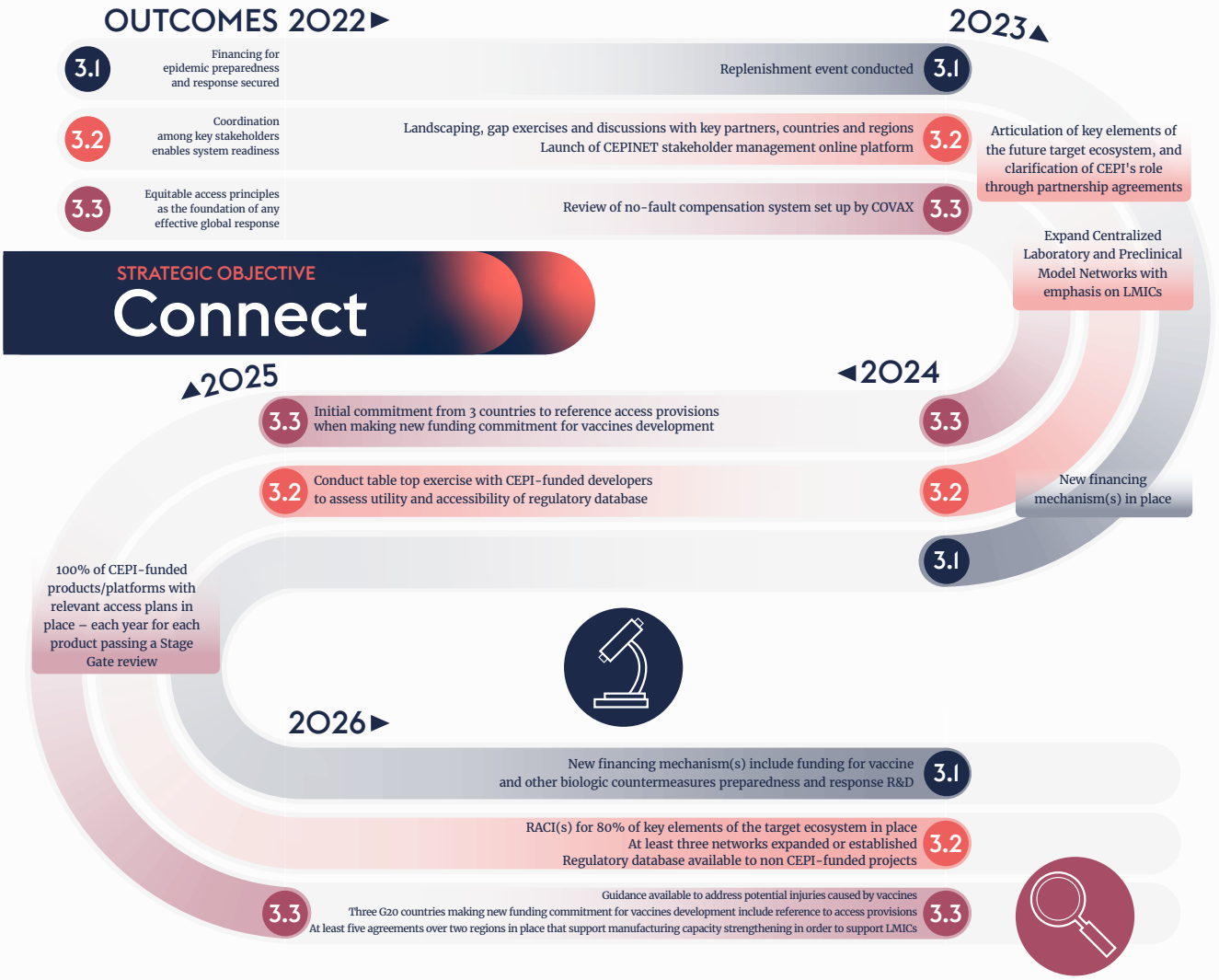
As a part of CEPI's strategic objective to **connect emerging infectious disease stakeholders to enable rapid countermeasure development, effective response and equitable access for those in need**, CEPI will focus on:

- Securing **financing** for epidemic preparedness and response
- Improving **coordination** among key stakeholders **to enable system readiness**
- Promoting **equitable access** principles as the foundation of any effective global response

Achieving these objectives will require working with, and through, partners.

[31] Ref. findings of the IPPR, the G7 "Pandemic preparedness partnership", the G20 HLIP and the GPMB.

Figure 4: Snapshot of CONNECT Roadmap to 2026



CEPI's Partnership Strategy

Delivering on CEPI 2.0 will require a coordinated approach from a broad range of partners, so partnership and stakeholder engagement will be critical to CEPI's success. CEPI will work with:

- Upstream research partners, to inform R&D priorities, identify emergency response partners, and trigger response activities.
- Product development partners, for products like priority pathogen vaccines and virus family vaccine candidate libraries, as well as partners for enabling science and coordinated manufacturing networks.
- Downstream implementation partners, to maximise the value and reach of investments by making sure they are deployed into a global system with pre-agreed governance, financing and allocation.
- Key policy partners, including governments; regional bodies; multilateral and financing organisations including the WHO, WTO, Gavi, UNICEF, PAHO; multilateral financing institutions; and civil society.

CEPI's Connect strategic objective is thus at the heart of how CEPI will operate – focusing on collaboration with others to achieve its mission, focusing on the right opportunities, developing state-of-the-art products and delivering these into a well-functioning ecosystem.

CEPI operates within a complex and rapidly evolving network of partners, including global health organisations, vaccine developers and manufacturers, academic institutions, governments, philanthropies, financial institutions, and civil society.

In this strategic period, CEPI will develop concrete plans for collaborations with specific partners, including through formal collaboration agreements (e.g., the MOU with the African Union), to identify shared strategic objectives and plans of action. For each activity under the CEPI 2.0 Strategy, relevant stakeholders will be mapped and CEPI will pursue strategic collaborations to correct any gaps and misalignments between CEPI investments and activities, and those of the broader ecosystem.

A key component will be regional engagement, building on existing partnerships with e.g., WHO and its regional offices, the African Union, development banks, and other organisations that support the development of regional infrastructure and expertise. The aim is to: strengthen capacity across LMICs; empower these countries to perform quality clinical studies and enabling science activities, as required to advance vaccine development (see the section "*Scale enabling sciences to further accelerate vaccine development*" for additional details); and support technology transfers and strengthen national and regional manufacturing capacity. CEPI will also engage with local and regional regulatory authorities to enable countries to take full ownership of their national health security.

Collaboration and partnership for the benefit of LMICs is core to achieving CEPI's strategic R&D priorities and central to CEPI's commitment to equitable access. LMIC engagement to identify national and regional level strengths and weaknesses is also core to CEPI's commitment to equitable access and sustainable manufacturing of vaccines and other biological countermeasures in LMICs.

BOX 9:
CEPI/African Union Partnership

The Memorandum of Understanding (MOU), signed with the African Union in April 2021 and executed with the Africa CDC, is a key example of how CEPI is working to strengthen its partnerships with LMICs. The MOU focuses on pandemic preparedness and response, expanding the availability of flexible, scalable and simple manufacturing across Africa, enhancing the availability and development of a flexible workforce across the value chain, and developing an ecosystem of clinical trial networks and labs.

As a first step, CEPI is actively supporting the Partnerships for African Vaccine Manufacturing (PAVM) towards improving the vaccine R&D-manufacturing value chain in Africa, both in terms of participation in advisory groups and through consultancy support for the Regulatory Strengthening, Technology & Intellectual Property and R&D Hubs, and Talent Development workstreams. CEPI is also supporting the Africa CDC through the provision of a secondee working within the PAVM secretariat.

Moreover, under this MOU, CEPI is working to leverage its survey on regional manufacturing capacity to identify and help address challenges relevant to PAVM's objectives. Other new areas for collaboration include CEPI's work with Africa CDC to help laboratories in the African continent join the CEPI Centralised Lab Network and exploring the possible expansion of the current CEPI epidemiological studies programme for the continent.

Secure financing for epidemic preparedness and response

The lack of readily available and sufficient funding mechanisms has been a major barrier to an effective response to the COVID-19 pandemic, particularly for low- and middle-income countries. Sustainable financing remains one of the biggest challenges for the future. The current model of financing is highly fragmented and unpredictable, and thus the response to date has had to rely on a major ongoing fundraising effort. Funding relies on discretionary aid contributions, predominantly from high-income countries, but also from philanthropic funders and, to a lesser degree, from private sources. Going forward, an end-to-end financing plan that creates the needed financing and incentives for product development, procurement and deployment, and enables other needed aspects of a global response, will be critical to preparedness for the next epidemic or pandemic crisis. The establishment of multilateral mechanisms, such as the Global Health Threat Fund, will be key to achieve this.

An essential condition for better R&D preparedness and response is the availability of funding. Product development is a continuous improvement cycle and, as such, the line between R&D preparedness and response is not always clear: each iterative cycle contributes to further advancement in R&D, manufacturing innovation and increased capacity. From a vaccine development perspective, activities such as building a library of prototype vaccines tested through Phase I clinical trials, can help to swiftly transition from 'preparedness' to 'response' by rapidly adapting those vaccines in an outbreak situation, before it is clear if the outbreak will reach pandemic or epidemic proportions. Hence, to ensure investments in preparedness R&D leads to a more efficient response, availability of ready releasable surge funding for early response R&D activities is key.

Findings from the COVAX Research & Development and Manufacturing Investment Committee (RDMIC) clearly outline how inadequate financing and the lack of advance purchase agreements for the global needs early on, slowed or inhibited vaccine R&D and ultimately product availability. It also underlines that other enabling science investments and actions are needed to make R&D investments more fruitful in terms of response, such as global standards for clinical trials and regulatory approvals.

Hence, future end-to-end mechanisms should secure funding for (i) R&D preparedness in the interepidemic/pandemic periods, and (ii) readily releasable 'surge' financing for product development in a crisis to cover R&D needs as well manufacturing 'at-risk' and advanced purchase commitments to facilitate equitable access to products.

G7 and G20 governments have highlighted the need for new approaches to financing the future architecture for pandemic preparedness and response. The G20 HLIP has called for an investment of an additional US$75 billion in financing to address gaps in pandemic preparedness and response. Achieving this level of financing requires political and financial commitment, including dedicated health security lines embedded in national budgets. It also requires participation from sovereign investors, as well as new and innovative financing mechanisms, for example, development bonds.

CEPI will be a strong advocate for a focus on R&D preparedness and response financing as part of the new initiatives being proposed, including the Global Health Threats Board, or similar setup. While CEPI's focus will be to secure grant financing through a traditional replenishment campaign in the short term, exploration for and development of long-term sustainable financing will take place in parallel, including around increasing commitments from both ODA and non-ODA eligible funding sources, both for CEPI's COVID-19 and core priority pathogen portfolios.

Advocate for availability of sustainable and ready releasable funding mechanisms

Driving the political commitment required for pre-agreed mechanisms for sufficient, sustainable, and rapidly available funding for the development, manufacture, procurement, delivery and equitable access to vaccines, therapeutics and diagnostics, requires an evidence-based investment case and action to fund it. To support this drive, CEPI will actively engage at the political and technical levels to:

- Promote strengthened coordination and financing mechanisms at the global level.
- Contribute to synergies between national, regional and global investments in R&D and manufacturing.
- Promote development of future financing instruments that can support advanced purchase agreements to enable at-risk manufacturing, as well as support geographically diversified manufacturing, working with financial institutions, regions and countries.

Coordinate among key stakeholders to enable system readiness

As COVID-19 has illustrated, there is a need to define clearer roles and responsibilities for key activities within pandemic preparedness and response. In the next five-year period, CEPI will leverage its role as a convener and thought leader to: highlight and address the gaps; strengthen global epidemic preparedness and response with respect to vaccine and related medical countermeasures research and development; and enable adaptive and harmonised R&D approaches.

Improving coordination requires a common understanding and a joint vision for the future ecosystem architecture. CEPI aims to work with partners to agree upon key elements of the future preparedness and response ecosystem, for example, by developing and aligning around what we have termed a "**target ecosystem profile**", based on the learning from ACT-A, COVAX and recommendations from the IPPR, the G7 PPP, the G20 HLIP and GPMB.

Critical elements of a target ecosystem include:

- Long term, sustainable, ready releasable financing mechanisms across the spectrum of preparedness and response, including development, manufacture, procurement and delivery.
- A library of prototype vaccines and other biological interventions against representative pathogens from the most critical viral families.
- An early warning and surveillance system that is linked to decision triggers for R&D as well as other public health mitigation measures in HICs and LMICs alike.
- A network of ready-to-act, funded entities operating across a set of core functional areas (e.g., detection, enabling sciences, clinical trials) in different geographic locations.
- Regulatory readiness to support rapid development, and expedited reviews and approvals of rapid response platforms, including adaptive clinical development plans and post-marketing assessment to support benefit-risk assessments.
- A sustainable global network of manufacturers, including in LMICs, with flexible capacity and technological capability to support global (or regional) demand.
- Institutional and legal readiness, including no-fault injury compensation mechanisms and provisions that address liability and indemnification concerns, to allow for distribution in all relevant markets.
- Mechanisms and governance to enable equitable access, regardless of the ability to pay.

For some of these key elements, CEPI will take a leadership role as described in the Prepare and Transform sections. For others, CEPI's interventions will be to support and inform. CEPI will continue to discuss requirements under each of these elements with key collaboration partners.

Fill gaps in the global R&D ecosystem for end-to-end epidemic preparedness and response

As part of defining a possible "target ecosystem profile", CEPI has identified multiple core activities where entities from all regions should be linked. Sustainable funding of these networks will be crucial to allow for "inter-epidemic" activity. These include networks for preclinical models, lab capacity for priority pathogens, standards and assays, systems immunology, serum and specimen collection, epidemiology, in addition to manufacturing (see the section "*Scale enabling sciences to further accelerate vaccine development*" for additional details).

With an emphasis on strengthening partnerships with LMICs, activities planned in this area include but are not limited to:

- Strengthening clinical trial networks with national partners and product development partnerships (PDPs) on multiple continents and leveraging synergies between research against neglected EIDs of outbreak, epidemic and pandemic potential.
- Working with organisations like DCVMN to strengthen partnerships to support technology transfer and coordinated manufacturing capacity.
- Encouraging partnerships between R&D companies and manufacturers to support innovations of scale and scope of particular importance for LMICs, for example affordable vaccines and biologicals and easy to deliver systems.
- Driving a global consultation and establishment of a global network for collection and sharing of specimens for assay development and evaluation at internationally recognised standards.
- Expanding the Centralised Laboratory Network and Animal Model Network, laboratory strengthening (GCLP training, Laboratory equipment) for priority pathogen vaccines and diagnostics.
- Investing to increase capacity and maintain high compliance standards with NC3Rs, cultivate a partnership with UK-NC3Rs through ongoing reviews and workshops with partners.
- Establishing a global community engagement practitioner network (CEPINET) to support vaccine research, development, and uptake.

Enable adaptive and harmonised R&D approaches

CEPI will promote "rules of the road" for R&D to facilitate the system-wide production of comparable data fit for rapid regulatory action in an outbreak. As such, CEPI will work with the WHO and other partners to support the development and pre-positioning of standard clinical trial protocols, template agreements, and infrastructure—particularly in LMICs—to enable rapid and clinically relevant implementation of research activities early in an outbreak, enhance agility to respond to an evolving outbreak, and increase equitable access to the R&D outputs. CEPI will also engage in global policy dialogues to create a shared vision of rapid, prioritised, and responsive R&D—and the pathways to achieve it. Key to this will be addressing impediments to the timely collection and sharing of biological samples, data, and analyses for the development of countermeasures.

CEPI will also support increased regulatory agility. This will include supporting local and regional regulatory authorities to develop ways of working based on best practices (from pandemic flu, Ebola, and COVID-19) for rapid scientific advice, accelerated/rolling review and approval timelines of clinical trials and emergency licensure for established and new technologies. CEPI will review where regulation unnecessarily slowed development or prevented developers from taking an informed risk; support the development of new emergency legislation or guidance to enable specific derogations of primary legislation in case of an emergency to avoid bottlenecks and barriers (e.g., GMO, independent batch release, packaging/labelling requirements); and provide greater regulatory support where developers need it (e.g., scale-up of production, GMP readiness, technology transfers and site changes, etc.).

In partnership with regulators, developers, DCVMN, EFPIA, IFPMA, WHO (including Regional Offices), and regional industry associations, CEPI will identify lessons learned to contribute to accelerating vaccine development and rapid access to innovative vaccines in LMICs. CEPI will engage with regulators and policymakers in LMICs to raise awareness of the need to develop new emergency guidelines and legislation and participate in their development as appropriate, for example by funding regional meetings.

All countries need fit-for-purpose emergency legislation, outbreak-ready regulatory pathways and, where possible, harmonised procedures and the ability to adopt regulatory review or recognise a trusted authority (e.g., WHO EUL) rapidly to get vaccine authorised faster. To support this, CEPI will work with the WHO to establish a transparent global database that maps country requirements and timelines to licensure and deployment of vaccines in an outbreak.

CEPI will also review other regulatory agency collaborating procedures (e.g., Project Orbis, Access Consortium, ICMRA) and work with national and regional regulatory authorities to identify opportunities to expand existing collaborations, including where a single point of review and approval can be recognised by multiple countries in parallel. Particularly in the case of highly sophisticated technology-based vaccines, CEPI will facilitate collaborations and ensure an appropriate level of technical support is provided to manufacturers and national regulatory authorities less experienced in dealing with highly sophisticated technology-based vaccines or vaccines new to the market in emergencies. CEPI will also support manufacturing facilities to have a culture of GMP readiness, ensuring they have been inspected early by stringent regulatory authorities to establish globally recognised issued GMP certificates.

Equitable access principles as the foundation of any effective global response

Fragile health systems with limited means to finance or ability to drive vaccine development and manufacturing has put LMIC populations at heightened vulnerability to emerging infectious threats. By working together with LMICs to develop and access vaccines and other countermeasures, CEPI aims to make a significant contribution to the Sustainable Development Goals (SDGs), specifically SDG 3—Good Health and Wellbeing—and put LMICs in the driving seat for developing interventions that will positively affect the health of their populations.

Fair distribution of vaccines means that appropriate vaccines are available to populations when and where they are needed to end an outbreak or curtail an epidemic. Equitable access takes the concept of availability and fair distribution a step further by requiring that distribution is de-linked from the ability to pay the same price as others, and that vaccines are introduced and rolled out in a similar timeframe to others.

COVID-19, however, has exposed the weakness of the global pandemic response which has failed to put equitable access to vaccines at its heart, thereby causing unnecessary and preventable loss of life and prolonging the pandemic. While it is a legitimate duty of a government to protect its population, the actions of countries putting national interest first, either by securing doses through requisition, export controls, or bilateral deals, has resulted in vaccines being distributed in a grossly inequitable fashion and has been a major barrier to ending the pandemic fairly and efficiently. Furthermore, global vaccine manufacturing capacity is heavily weighted towards the global north and a small number of other countries which gives those nations and regions a significant advantage in controlling the distribution of vaccine output, to the detriment of the majority of countries that do not have this capability.

Achieving equitable access to vaccines for future pandemics, therefore, requires strengthened public and private commitment to equitable access, and a renewed focus on increasing the geographical diversity of vaccine manufacturing capacity—particularly in LMICs—so that all regions can take control of their health security.

Strengthen public and private commitment to equitable access

In a scenario of scarce supply, the manufacturer holds almost all the leverage, balanced only by high-income countries willing to pay early and at-risk for procurement. Embedding equitable access in early funding terms for R&D is a powerful tool to enable LMIC access. Most charitable funders of medical technology already include terms requiring steps to be taken to achieve equitable access. However, most government funding terms do not, as they focus entirely on securing domestic supply for their population. Government funding accounts for a significant proportion of annual R&D spend, so this is a significant missed opportunity to secure additional leverage in favour of equitable access. A shift from viewing government-funded R&D as being primarily or exclusively for the benefit of domestic and/or regional constituents, to one which addresses problems of global health, would have major implications for global equitable access. CEPI will therefore promote the adoption of a minimum set of equitable access requirements in all new public funding and procurement arrangements for vaccines by G20 and other significant government funders.

The lack of appropriate risk-sharing mechanisms is another significant barrier to supply LMICs. The industry will not supply the novel countermeasures needed in a pandemic without such mechanisms. During the COVID-19 pandemic, mechanisms for indemnity and liability for vaccine use, including a no-fault compensation plan for LMICs, were built from scratch by the COVAX partners working with industry and countries. CEPI will work with key stakeholders to build on these risk-sharing mechanisms developed for COVAX AMC participants so that they can be implemented faster in the future, enabling speedier procurement for LMICs in outbreak situations.

CEPI will work with key stakeholders including LMICs, economists, epidemiologists and health security experts to assess demand for vaccines both at an early stage and at appropriate points during the development to facilitate rapid uptake. This demand assessment will look at likely deployment in an outbreak situation and whether there is also demand for a longer-term endemic use. The assessments will enable CEPI to target R&D and preparedness activities appropriately and to prepare for the rapid deployment of vaccines in an outbreak scenario. Where there is a demand for an endemic vaccine, CEPI will work with appropriate procurement bodies so that they can minimise any time delay between marketing approval and procurement for LMICs.

Furthermore, CEPI will strengthen strategic engagement with industry on vaccine and biological countermeasure development and response to EIDs. The industry is an indispensable player in vaccine research and development, so CEPI's engagement with the industry is crucial to the success of CEPI 2.0. The industry provides significant R&D funding, but it also shoulders the bulk of the investment risk. As industry must act in an economically viable way, public funding is key to driving R&D in scenarios of insufficient or uncertain markets for a product. CEPI intends to continue to fund R&D in return for access to the technology for LMIC supply in the case of insufficient/uncertain markets for the end product. This is often the case for pathogens which, whilst not endemic, may give rise to an outbreak, as exemplified by the WHO R&D Blueprint list.

However—as in the case of COVID-19—there are scenarios where the initial market is too uncertain to predict, making early industry investment unviable, but where the market becomes clear over time, and industry investment then becomes viable. In such circumstances, CEPI may still fund R&D in return for access to doses for LMICs in a comparable timeframe to other supplies and at an affordable cost. CEPI's non-dilutive funding can help generate new innovative technologies or products that might not otherwise be funded, for both disease areas of interest to CEPI, as well as disease areas of interest to industry partners, whilst facilitating the improved deployment of vaccines and other biologic countermeasures in LMICs. CEPI will enable technology transfer to broaden the supply chain with a view to increasing the economic viability of the programmes it funds and driving manufacturing and improving health security in the global south. CEPI's work on harmonising and streamlining regulatory pathways, target product profiles and demand assessment, will all form part of a sustainable and synergistic engagement with industry.

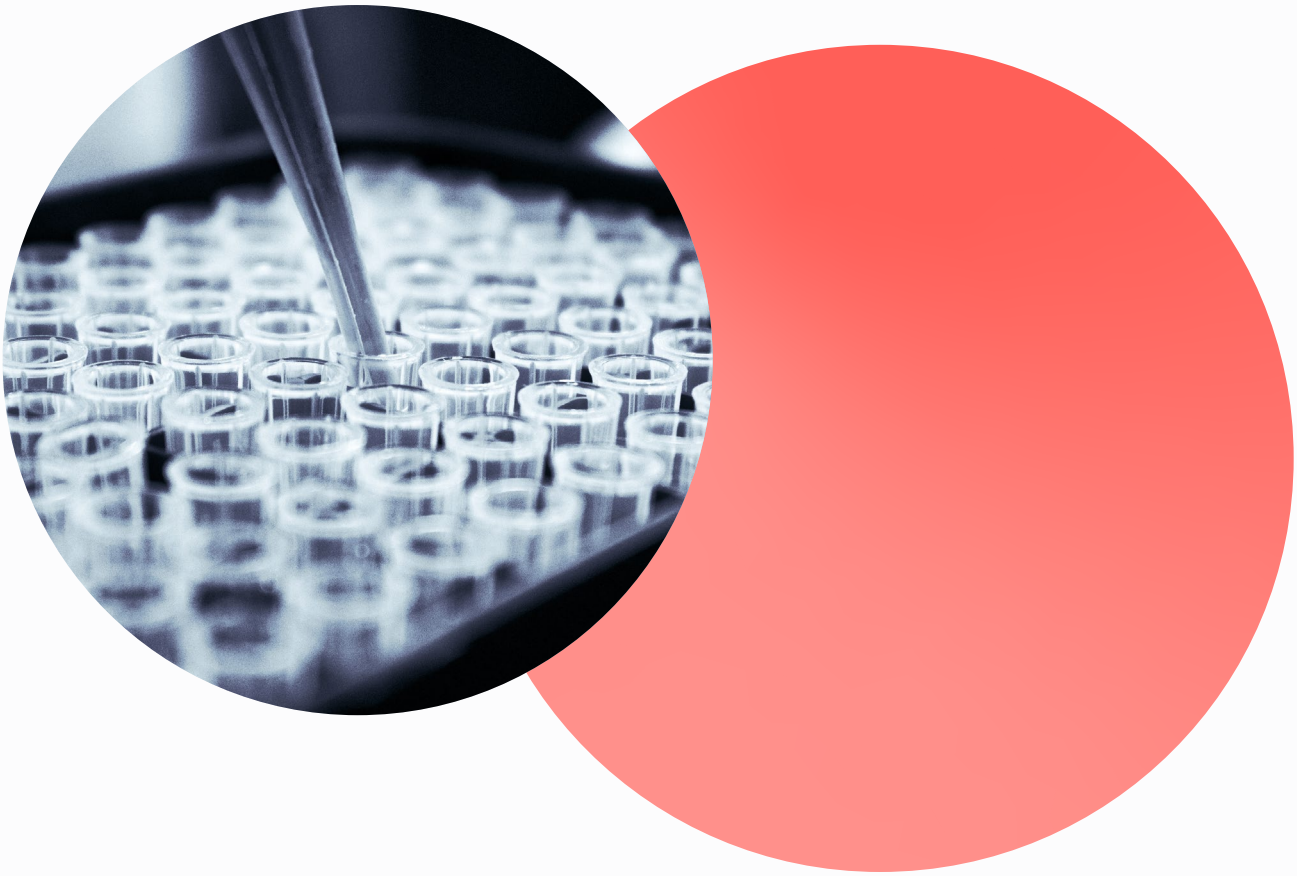
CEPI also aims to strengthen partnerships with the two main manufacturing associations, the IFMPA and DCVMN and engage with the World Economic Forum and Global Business Coalition, among others, to catalyse action on equitable access and leverage investments in low- and middle-income countries for all aspects of R&D and manufacturing.

BOX 10:

Equitable Access Case Study | Ensuring equitable access through no fault compensation (NFC) scheme

In February 2021, COVAX entered into an agreement with Chubb Limited (NYSE:CB) through ESIS Inc., a Chubb Company for the administration of a no fault compensation programme covering individuals who experience adverse serious events associated with COVAX distributed vaccines. This programme currently runs up to June 2022 with a possibility of a period extension. CEPI will work towards similar programmes for future situations in LMICs as part of the Connect Pillar.

- Based on the confidence in the safety of vaccines distributed through the COVAX facility, the programme provides a vaccine injury compensation mechanism that's robust, transparent, simple, free and independent for individuals in LMICs. This serves to counter vaccine hesitancy by allaying safety concerns among populations.
- Available in 92 LMICs and economies eligible for support through the COVAX advanced market commitment facility.
- Improves equitable access to supply, especially for countries without their own compensation programme by de-risking manufacturers where there are concerns over indemnity and liability; hence an incentive to supply LMICs.



Diversify global manufacturing capability geographically

The COVID-19 pandemic has highlighted the risk of any one region or country dominating the supply of vaccines. The geographical diversity of global manufacturing capacity is therefore critical to both pandemic preparedness and response. Recognising that the bulk of innovation currently comes from manufacturers in the global north, CEPI is committed to driving innovation and manufacturing in the global south. This will entail supporting a range of activities from technology transfer, to providing know-how and training and development of a qualified workforce and including stringent provisions in partner development plans both around access and supporting local capacity development. CEPI is already supporting this through the COVAX Manufacturing Taskforce WHO-led Workstream 3, which is focused on establishing and expanding vaccine manufacturing capacity and capability in LMICs—which predominate in the southern hemisphere. CEPI is also working together with WHO HQ (e.g., the local production assistance unit) and WHO regional offices, following the 74th World Health Assembly decree for WHO to lead on improving and strengthening pharma/vaccine manufacture per region. Over time, this focus on the sustainable growth of local capabilities and infrastructure should bring economic growth and increased health security to those regions as well as ensure that vaccines are available in sufficient capacity and in real-time when an outbreak occurs.

CEPI will support the further development of manufacturing capacity in LMICs by leveraging strategic alliances, including that of funders and investors, to build an integrated, scalable, on-demand network of regional private and public manufacturing facilities to rapidly meet future global vaccine demand. CEPI will build a network of centres of excellence globally that will champion R&D, manufacturing, clinical, regulatory and distribution among all other key elements of the preparedness value chain e.g., CEPI is already actively supporting the Partnerships for African Vaccine Manufacturing (PAVM) towards improving the vaccine R&D-manufacturing value chain in Africa (see Box 9 for additional details).

As a first step, in partnership with several global ecosystem stakeholders, CEPI will utilise its recent Regional Manufacturing Request for Information 2021 (RFI 21) data to develop specific manufacturing strategic roadmaps for each region and prioritise the activities aimed at improving overall preparedness and response to epidemic/pandemic outbreaks in LMICs. CEPI plans to link together this network of vaccine manufacturing centres of excellence by supporting the development of global partnerships to enable sustainable on-demand manufacturing. CEPI will also partner with the DCMVN and other LMIC manufacturers to support in-bound technology transfers and promote innovation to further increase sustainable manufacturing capability.

An important prerequisite for the ability to scale and diversify manufacturing is a transparent and functioning supply chain. Vaccine manufacturing processes are highly complex and expanding manufacturing capacity requires managing intricate cross-border supply chains, which frequently involve more than 100 components.

During COVID-19, the historic scaling up of manufacturing, which aimed to triple previous annual vaccine outputs, created supply chain bottlenecks which led to acute shortages of vital supplies. These prevented COVID-19 vaccine manufacturers from operating at full capacity, delaying production and contributing to inequity.

To tackle this challenge CEPI implemented the COVAX Marketplace (see Box 11), which aims to respond quickly to immediate market needs, resolve bottlenecks and improve the free flow of critical COVID-19 vaccine supplies. As a platform for vaccine manufacturers and suppliers to offer or request critical supplies, the COVAX Marketplace is an example of how CEPI is able to resolve challenges by connecting partners and providing innovative solutions.

BOX II:

The COVAX Marketplace

The COVAX Marketplace is a key deliverable of the COVAX Manufacturing Task Force. It aims to respond quickly to immediate market needs and bottlenecks and improve the free flow of critical COVID-19 vaccine supplies by:

- Providing suppliers with a platform to allocate and reallocate unused materials.
- Mobilising idle stock from vaccines and candidates that fail prior to gaining regulatory approval – as well as from those that might scale down their production in the future.
- Mobilising potential surplus stock from manufacturers with non-vaccine activities.

The COVAX Marketplace provides a secure platform for vaccine manufacturers and suppliers of critical inputs to confidentially indicate their needs or available supplies to CEPI, in its role as facilitator of the Marketplace. CEPI will identify matching offers and requests and connect potential matches, prioritising matches based on objective criteria including whether the manufacturer has a COVAX advance purchase agreement and WHO Emergency Use Listing (EUL), as well as dose volumes and delivery timings.

The initial version of the Marketplace includes COVAX vaccine manufacturers and suppliers of the key materials that have been identified as being most urgently needed.

Participants in the COVAX Marketplace will be able to offer and/or request any materials required for vaccine production, but it will initially focus on six categories of supplies that have been identified as critical: bioreactor bags, single use assemblies, cell culture media, filters, lipids, vials, and stoppers.

CEPI will explore extending the Marketplace to include additional participants and supplies required to manufacture other lifesaving therapies and vaccines that are also being affected by current global supply shortages.

July – November 2021 highlights:

- 50+ partners expressing interesting in using the Marketplace
- 15 partners hosted on the Marketplace
- 8 offers posted
- 3 requests posted
- 3 matches

Performance management and monitoring of the Connect strategic objective

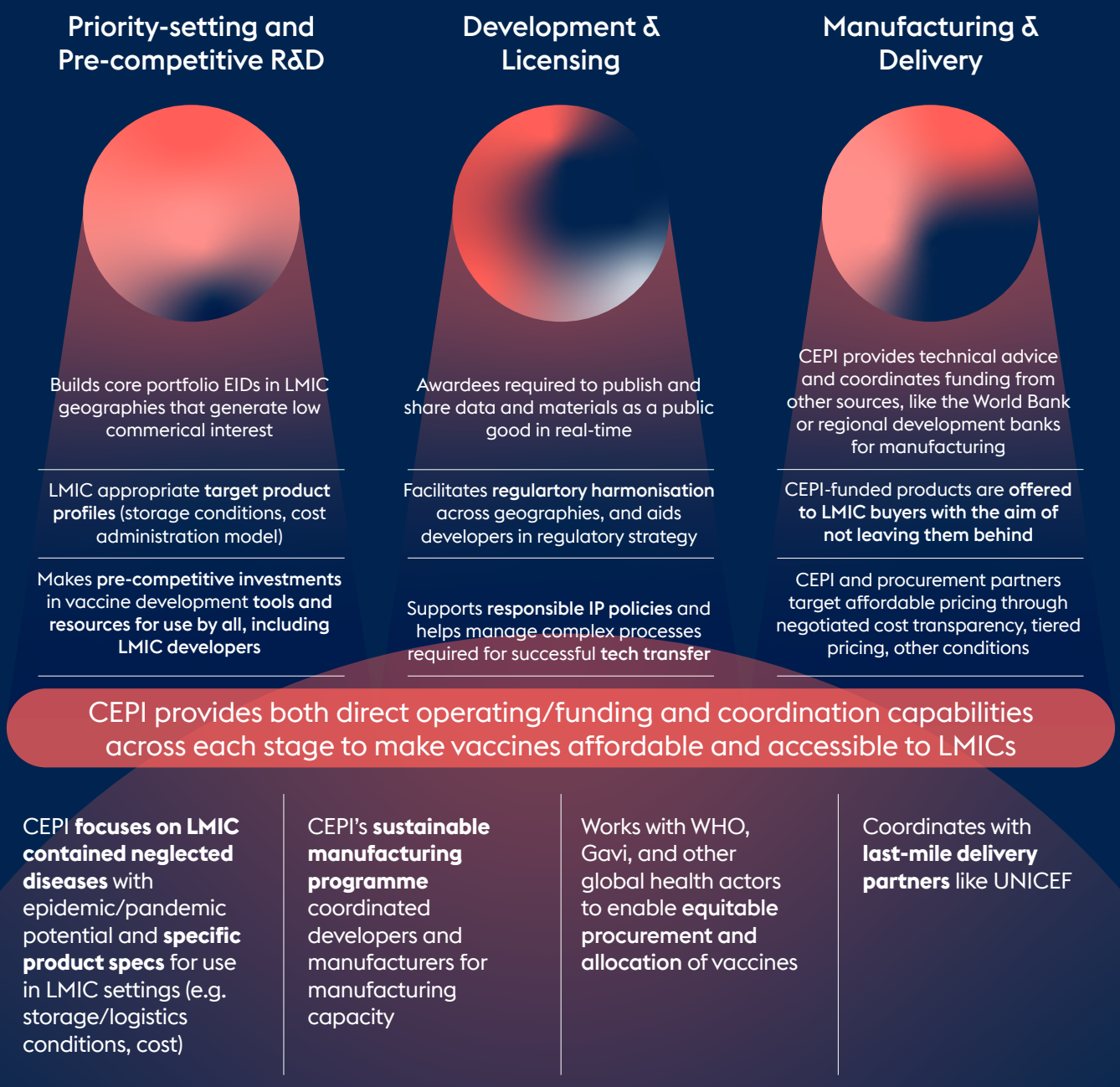
CEPI will measure its performance towards the Prepare strategic objective using the following draft Key Performance Indicators (KPI) and Targets per Outcome (OC) and Output (OP), in the CEPI 2.0 strategic period 2022-2026:

- OC 3.1: Financing for epidemic preparedness and response secured.
  KPI: New financing mechanisms include funding for vaccines and other biologic countermeasures preparedness and response R&D.
  Target: Funding for vaccine and other biologic countermeasures preparedness and response R&D
  - OP 3.1.1: Sustainable and ready releasable funding mechanisms available.
    KPI: CEPI fully funded for 2.0.
    Target: USD 3.5 billion in commitments
- OC 3.2: Coordination among key stakeholders enables system readiness.
  KPI: Alignment on key elements of a target ecosystem to accelerate development and promote equitable access of emerging infectious disease countermeasures.
  Target: RACI(s) for 80% of key elements in place
  - OP 3.2.1: Gaps in the global R&D ecosystem for end-to-end epidemic preparedness and response filled.
    KPI: Number of identified areas with funded global networks established (or expanded).
    Target: At least three networks expanded or established
  - OP 3.2.2: Adaptive and harmonised R&D approaches enabled.
    KPI: Regulatory database available and accessed by developers.
    Target: Database available as a pilot to CEPI-funded developers by 2023 with view to wider roll out towards 2026
- OC 3.3: Equitable access principles as the foundation of any effective global response.
  KPI: Removing at least one key systemic obstacle to access for LMICs.
  Target: At least one
  - OP 3.3.1: Public and private commitment to equitable access strengthened.
    KPI: Percent of CEPI funded products/platforms with relevant access plans in place.
    Target: 100% each year for each product passing a Stage Gate review
  - OP 3.3.2: Global manufacturing capability geographically diversified.
    KPI: Number of agreements in place that support manufacturing capacity strengthening in order to support LMICs
    Target: At least five over two regions

Equitable Access

The principle of equitable access is at the forefront of CEPI's decision-making process, from the moment a vaccine candidate is assessed for funding to the moment it is procured and distributed by other organisations (see Figure 5). CEPI is singularly focused on ensuring the vaccines and targeted biologic countermeasures whose development it supports are appropriate for use and easy to deliver in low-resource settings.

Figure 5: CEPI's end-to-end approach to enable equitable access to date



Where there is insufficient or too uncertain a market to support significant industry R&D investment, CEPI focusses its access efforts on sustainable and affordable access to technology for supply to LMICs and enables other countries' preparedness through the existence of a product.

Where there is a sufficient market to support significant R&D investment, CEPI focusses its efforts on access to doses for LMICs in a timely manner at an affordable cost and on enabling activities for other countries' access to doses through its global view and activities on sustainable manufacturing and enabling science.

CEPI's focus on enabling global equitable access to vaccines and targeted biologic countermeasures permeates through all aspects of the CEPI 2.0 Strategy and will continue to build on the approach illustrated in Figure 5 above. These equitable considerations are summarised below for each of CEPI strategic objectives.

Equitable access considerations for Prepare

Under the Prepare strategic objective, CEPI will enable equitable access by funding the development of vaccines and other medical countermeasures where no suitable products exist and where the market is unlikely to deliver them. CEPI will embed equitable access as a core component of its funding agreements, in line with its Equitable Access Policy, and when selecting products in which to invest, CEPI will look for formulations, presentations and cost profiles suitable for use in LMICs, given climate, supply chain logistics and cost constraints. Specifically, CEPI will:

- **Leverage its vaccine development funding to enable equitable access by embedding access requirements into all vaccine development partnerships**. These requirements will be focussed on achieving the core outcomes stated above and will be commensurate with the stage and level of investment.
- **Facilitate dialogue and engagement with regulatory agencies to overcome challenges associated with obtaining regulatory marketing approval for high-risk pathogens in the country of use.** CEPI will obtain and support partner commitments through marketing approval, including WHO prequalification, as CEPI has a particular interest in access for LMICs and WHO prequalification is a key step towards use in those countries.
- **Continue to invest in Enabling Sciences and broaden R&D capacity-strengthening activities**. CEPI's enabling science programme provides the tools and knowledge for developers all over the world, including those in LMICs, to accelerate their programmes and make smarter development decisions. It is designed to benefit vaccine developers throughout the world, including those which are not part of the CEPI portfolio.
- **CEPI will also increase the ability of regions and countries to take control of their own vaccine development** in future by strengthening research and development capacities in LMICs, including clinical trial sites for efficacy studies, and funding enabling science and clinical trials in those territories.
- **Ensure all manufacturing output corresponding to the CEPI-funded part of COVID-19 vaccine development are to be offered first to the COVAX Facility; and accelerate the availability and affordability of COVID-19 vaccine doses for COVAX through grants and loans to help developers scale up and scale out production and secure raw materials.** CEPI will continue to enable low pricing by requiring developers to offer early doses to Gavi for the COVAX Facility, by sharing the risk of inventory build (in products not yet approved for emergency use listing) and by using its leverage in early-stage investments to secure commitments to pricing levels/formulae consistent with CEPI's Equitable Access Policy. If the COVAX Facility is not able to enter into purchase agreements for CEPI-supported vaccines as anticipated, CEPI has the right to redirect the supply to another public sector procurer. CEPI will continue to facilitate the COVAX Marketplace to address supply chain bottlenecks which could impact the availability of doses for COVAX.

- **Drive sustainable regional approaches to manufacture products.** Ultimately, to reach the end user, products must be produced, sold and deployed in the appropriate volumes when and where they are needed and regardless of ability to pay. For most developers, that will involve scaling up the manufacturing process and, for some, it will also mean scaling out, like the arrangement for the Chikungunya vaccine between Valneva and Butantan, with a technology transfer agreement to an LMIC by an LMIC manufacturer. CEPI will continue to drive for sustainable regional approaches to manufacturing products such as technology transfers, as well as tiered pricing frameworks. Where, as in the case of Chikungunya, MERS, SARS-CoV-2 and broadly protective coronavirus vaccines, a dual market exists or is likely for a potential vaccine, CEPI will take a cost-sharing approach to funding which supports access for LMICs and ensures WHO prequalification of vaccines to allow access in LMICs. In some cases, a stockpile may be secured to address any outbreak promptly.

- **Plan for project and supply continuity.** By advancing multiple candidates towards licensure, CEPI contributes to supply diversity which could result in a more competitive market with lower prices, as well as removing the risk of failure posed by single source supplier. Similarly, CEPI will continue to plan for project and supply continuity, including – in the absence of safety or technical concerns – having the right to continue the project if the original partner is unable to proceed and all other continuity plans have failed.

- **Consider factors beyond speed of development, such as storage conditions, method and route of administration, cost of goods, and number of doses required when making investment decisions.** Where vaccine development is happening (for example SARS-CoV-2), the profiles of many existing candidates are not optimal for LMIC deployment nor have they been made available in sufficient quantities to meet demand. CEPI takes the needs of LMICs into account in all its vaccine development. For SARS-CoV-2 in particular, CEPI aims to deliver at least two vaccines against variants of concern with a favourable profile for use in LMICs; and provide clinical proof of concept for two broadly protective SARS-CoV-2 candidates which are also suitable for LMIC use.

- **Where supply is insufficient to meet demand, maximise every dose by funding studies to explore new ways of using the doses available.** Shortages in the supply of vaccines have been a particular problem for low-income countries. Examples of potential solutions include heterologous prime-boost studies (known as ‘mix n match’ studies in which patients receive two different COVID-19 vaccines) and fractionation of vaccine doses (e.g., approximately half of a standard dose). Investment in clinical studies has proven to be a particularly successful tactic, for instance with Ebola: whilst the availability of two licensed Ebola vaccines improved supply security for a vaccine primarily used for outbreak control in sub-Saharan Africa, CEPI has filled a gap by funding studies which could expand access in vulnerable populations (e.g., pregnant women, children) who are often left out of clinical trials.

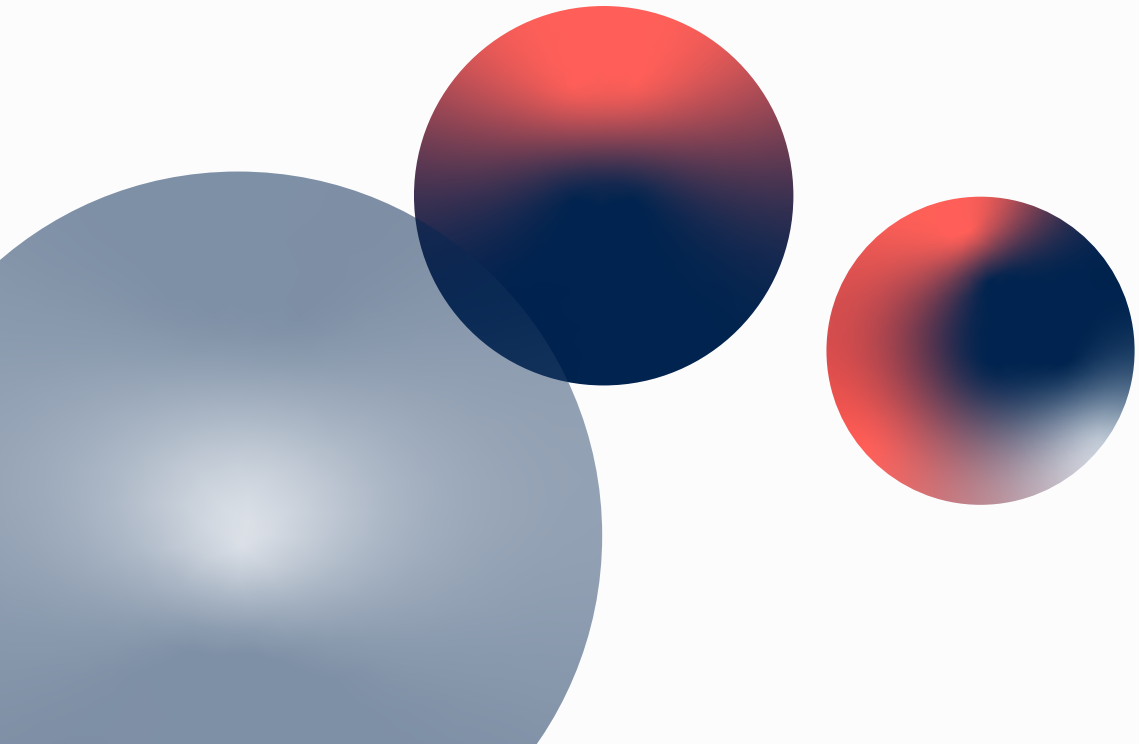
Equitable access considerations for Transform

Under the Transform strategic objective, CEPI will enable equitable access to innovative technologies including the development of prototypic vaccine candidates for multiple virus families with profiles that prioritise the ease of manufacture at scale, the cost of goods and the product characteristics, formulation and presentation for low-resource settings. When funding the development of innovative technologies, CEPI will embed equitable access as a core component of its funding agreements, in line with its Equitable Access Policy, which will enable use of technology to respond to appropriate outbreaks and supply of vaccines at affordable prices to LMICs.

Specifically, CEPI will:

- **Enable equitable access for funded innovative technologies for use within the same virus family during an outbreak and for endemic use in LMICs.** If an outbreak of a novel pathogen occurs, CEPI's funding agreements will contractually commit vaccine developers to conduct further research and development as needed to develop an appropriate vaccine as fast as possible and to provide specified supply for LMICs. For an endemic disease, CEPI's contracts will include access to technology or supply for affected territories. In each case, CEPI's contracts will include requirements for access and supply to LMICs at an affordable price, which is sustainable for the manufacturer. Since the ultimate price of vaccines is informed by both the cost of manufacture and the cost of supply to, and deployment in, the receiving country, CEPI will continue to focus on manufacturing innovations which result in lower cost-of-goods, and those which enable manufacturing to take place closer to the outbreak.
- **Bring manufacturing closer to the outbreak to reduce LMIC reliance on HIC manufacturing and mitigate restrictions on the free movement of goods between countries if the raw materials are also available.** Depending on the nature and scale of the outbreak, this could include early contracting to secure manufacturing closer to the location where the outbreak has occurred, enabling technology transfers, and deploying innovative or mobile manufacturing solutions, such as the mobile vaccine printer. Moving manufacturing closer to the outbreak improves free movement of product and local health security and could lead to a reduction in the cost of supply. Where this is by technology transfer, CEPI will consider how this transfer could improve the sustainability of local manufacturing capabilities and capacity, and how it would work with existing mechanisms that facilitate the voluntary sharing of intellectual property.
- **Fund sustainable solutions (e.g., technology transfer) that increase health security globally and for LMICs.** When a platform technology is concerned, there may be heightened sensitivity on the part of industry partners in sharing that technology or making long term commitments. The right voluntary licensing and knowledge exchange with the right technology transfer partner, brokered by CEPI, will be critical in achieving a sustainable solution.
- **Secure public benefit whilst keeping costs low for LMICs (e.g., economic benefit generated through sales to LMICs will be excluded from profit sharing).** Since CEPI invests public money, there must be a public good resulting from the use of that money. If the exploitation of intellectual property, know-how and other assets arising from a CEPI investment generate an economic benefit, CEPI will look to agree a share of that economic benefit with the awardee, and any economic benefit generated through sales to LMICs will be excluded to keep costs low for LMICs. CEPI's share of economic benefit may depend on multiple factors, including the timing and proportion of funding provided by CEPI for the underlying technology, and can be met through both cash payments or other contributions, including the donation of doses or a commitment to future work as appropriate.

- **Invest in Enabling Science activities, using existing laboratory capacities and infrastructure, and strategically strengthening capacity in LMICs, including between outbreaks, so that they are available, when needed, for all.** CEPI's enabling science programme provides the tools and knowledge for developers all over the world, including those in LMICs, to accelerate their programmes and make smarter development decisions. It includes multiple tools and data, required for accelerated vaccine/countermeasure development which can be categorised as:
  - Data from studies as part of development of a product candidate
  - Laboratory standards, reagents and tests and the global laboratory network to develop and deliver them
  - Epidemiological data
  - Clinical trial sites ready for testing countermeasures against the relevant pathogen
  - Community engagement, without which the data and the trial sites will not move forward
  - Regulatory landscape (referred to under both the Prepare and the Connect objectives). Each of these plays a crucial part in good science and the acceleration of development efforts focused on priority pathogens. For many countries, access to specialised laboratory capacities through CEPI will mitigate the lack of such resources and promote inclusion of all countries in the vaccine development field.
- **Implement country-led epidemiological studies in LMICs to support community engagement and capacity strengthening and prepare for potential future clinical trials.** These activities will facilitate the selection of clinical trial sites in LMICs for late-stage clinical studies and inform potential future vaccination strategies.
- **Focus clinical strategies on national regulatory agencies and National Immunisation Technical Advisory Group (NITAG) in LMICs, by including special populations of relevance in LMICs in these clinical development plans and benefit/risk assessment strategies.**
- **Engage with regulators and policy makers in LMICs to raise awareness of the need to develop new emergency guidelines and legislation and contribute as appropriate.**
- **Continue its commitment to open access publication of results so that everybody can benefit from the work that CEPI funds.**



Equitable access considerations for Connect

Under the Connect strategic objective CEPI will ensure that equitable access considerations for the Prepare and Transform strategic objectives described above form a central tenet of CEPI's Partnership Strategy, while also seeking to strengthen public and private commitment to equitable access.
Specifically, CEPI will:

- **Minimise systemic obstacles to equitable access by promoting alternative approaches to existing practices which could help level the playing field for LMICs**. These include promoting the adoption of a minimum set of equitable access requirements in all new public funding and procurement arrangements for vaccines by G20 and other significant government funders; and working with partners to build mechanisms for indemnity and liability for vaccine use in LMICs, enabling faster procurement for LMICs in outbreak situations.
- **Enable use of CEPI-funded products in LMICs in a timely manner** by assessing endemic and outbreak demand and coordinating with LMICs, Gavi, and WHO, among others, for the rapid deployment of vaccines in an outbreak scenario.
- **Strengthen strategic engagement with industry on countermeasure development and response to EIDs,** to catalyse action on equitable access and leverage investments in LMICs for all aspects of R&D and manufacturing.
- **Promote sustainable diversified manufacturing for CEPI-funded programmes.** CEPI will drive innovation and manufacturing in the global south by supporting a range of activities from technology transfer, to providing know-how, to training and development of a qualified workforce and including stringent provisions in partner development plans both around access and supporting local capacity development. CEPI will support the further development of manufacturing capacity in LMICs by leveraging strategic alliances, including that of funders and investors to build an integrated, scalable, on-demand network of regional private and public manufacturing facilities to rapidly meet future global vaccine demand.

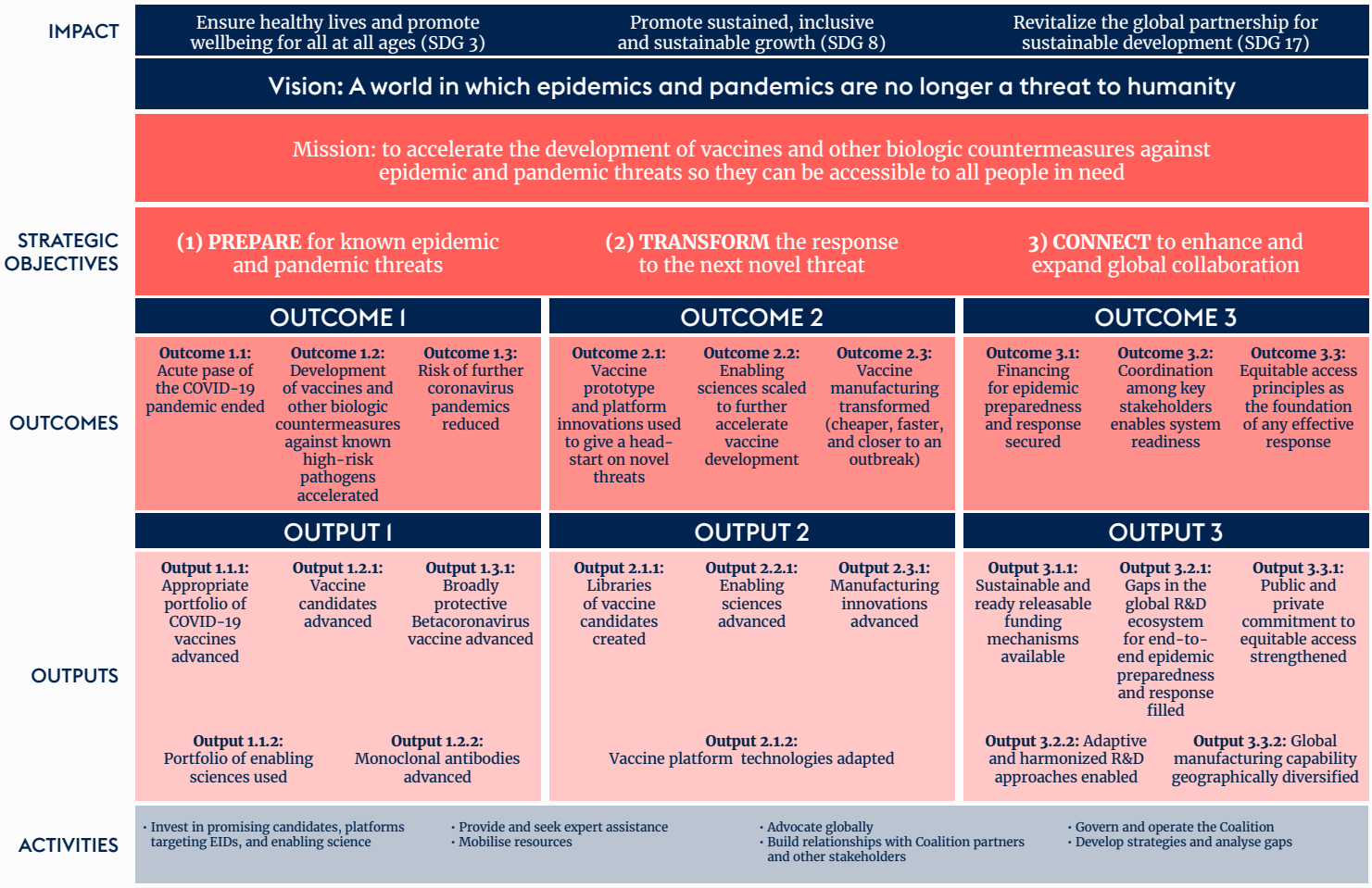
Results Framework

The CEPI 2.0 Results Framework serves as a summary of the strategy and explains how it will be achieved and how progress towards the goals will be measured. This is visualised through a Theory of Change with associated Results Framework that details expected outcomes and outputs and provides clear definitions and targets to measure progress on achieving CEPI's goals and objectives. The Results Framework strengthens accountability for what CEPI is aiming to deliver, by defining and measuring progress.

As CEPI and the external landscape CEPI operates in continues to evolve, indicators may be added or revised, following consultation with our investors. Additionally, as a learning organisation, during the implementation of the 2.0 strategy, CEPI may need to adapt its programmes which would require adaption of some of the indicators in this framework to ensure they are fit for purpose and measure progress towards the overarching strategy.

The Results Framework with Key Performance Indicators is an addendum to this Programme Document which is published on CEPI's website.

Theory of Change



Operating Model and Governance

To date, CEPI's operating model has successfully helped navigate a complex environment of stakeholders, aligned the organisation towards a common goal of executing the vision, and formed the foundation for a robust and effective pandemic response.

CEPI 2.0 will build on this position of strength, while identifying and implementing some targeted changes to ensure the operating model continues to enable CEPI to deliver against its vision as the organisation, its scale and scope evolves and expands. In this context, a systematic review of CEPI's operating model was initiated ahead of CEPI 2.0 to:

- Preserve and reinforce CEPI's core strengths as it grows in size and scope
- Embed positive change and lessons learned from the COVID-19 response
- Address targeted operational or capacity challenges

A holistic and comprehensive review of the operating model was undertaken involving all-staff listening sessions and interviews across CEPI's leadership team. The five dimensions of Structure, Governance, Ways of Working, Systems & Processes, and People & Places were examined, and the following recommendations proposed in preparation for CEPI 2.0:

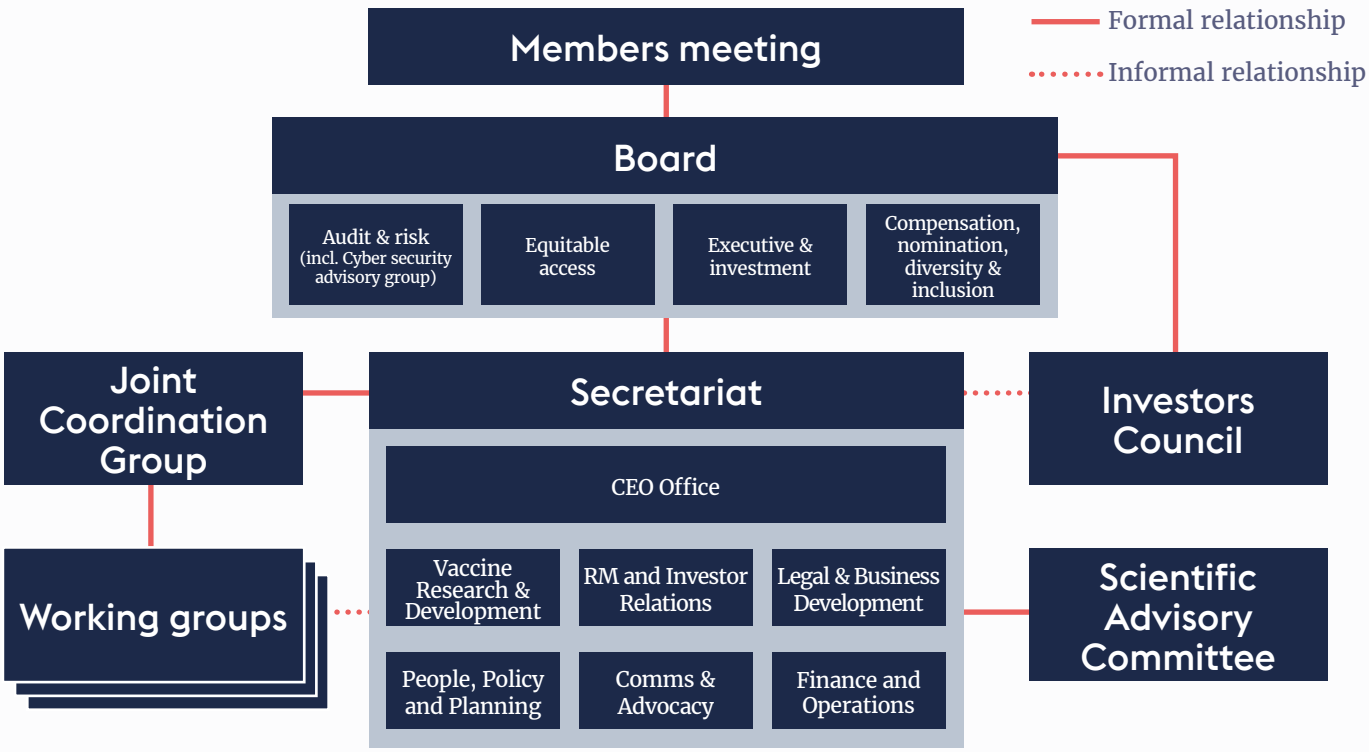
- **The right organisational structure**, streamlining the internal functions and with added senior management capacity to drive new and expanded focus areas, including the manufacturing agenda and CEPI's heightened external ambitions
- **A comprehensive governance architecture** which combines comprehensive oversight and scrutiny of decision making whilst retaining the agility which has been core to CEPI's decision-making
- **Retention of CEPI's flexible and agile ways of working**, enabling the organisation to tackle cross-functional challenges that require the whole organisation to work together as CEPI expands in size
- **Well documented, robust and effective process architecture** to support consistently strong decision making with the right oversight, backed up by fit-for-purpose systems integrated across all departments
- **Best-in-class people supplying the expertise that CEPI needs**, with the infrastructure set-up to attract the right global talent, with deliberately diverse representation across a range of backgrounds, geographies and expertise

The operating model review and identification of potential refinements
to enable progress against CEPI 2.0 objectives has been progressing successfully throughout 2021 and is on track for completion in early 2022.

Governance

CEPI's governance is designed to ensure a rigorous decision-making process, supported by the right expertise, and inclusive of important stakeholders. The existing model has served the organisation well to date, proving adaptable, effective and agile, particularly through the COVID-19 response. In part, this has been due to small adaptations as CEPI has evolved, including following the 2019 Board Effectiveness review. The CEPI governance structure is set-up as visualised below:

Figure 6: CEPI's Governance Structure



There are four permanent bodies at the heart of CEPI's governance system. These are:

- **The CEPI Board** that holds responsibility for all major decisions (other than those reserved to the Members Meeting), including all investment decisions exceeding US$5M. The CEPI Board is composed of 12 members representing academia, industry, government, NGOs. The Board is supported by four sub-committees to inform core decisions: the Executive and Investment Committee, the Nominations, Compensation, Diversity and Inclusion Committee including a dedicated advisory group on cyber security, the Audit and Risk Committee, and the Equitable Access Committee.
- **The Investors Council**, consisting of CEPI's funders, has the right to approve investment proposals exceeding $100M before a decision is made by the Board. In addition, the Investors Council receives regular updates from CEPI, shares information, provides guidance and oversight of CEPI activities, and engages in resource mobilisation efforts.
- **The CEPI Members Meeting**, composed of the voting members of the CEPI Board and the members of the Investors Council, has responsibility for adopting the annual accounts and making amendments to the Articles of Association.
- **The CEPI Leadership Team**, led by the CEO is responsible for the day-to-day running of CEPI under the direction of the Board. This includes responsibility for investment decisions of less than US$5M.

In addition, other expert committees support CEPI's mission, including:

- **The Scientific Advisory Committee (SAC)**, founded in 2018 to provide world-class scientific input and recommendations to CEPI staff and the Board. The recently renewed and expanded committee is composed of 35 recognised experts with knowledge and experience in areas relevant to CEPI's activities. Its roles include advising on the scope of CEPI's global outbreak preparedness objectives, sharing advice on the latest research and innovation in vaccine technology, advising on CEPI's current portfolio, and supports the creation of additional Calls for Proposals.
- **The Joint Coordination Group (JCG)**, a roundtable of 10-15 independent institutions with an interest in CEPI's activities, come together to discuss how CEPI can enhance its efforts to deliver and deploy vaccines by addressing challenges relating to R&D, regulation, procurement, stockpiling, and delivery. As well as helping to advance the overall stewardship of our portfolio, this group informs the broader field of vaccine development and preparedness.

Internally, CEPI has two core committees to support the CEO to make agile and effective decisions, enabling day-to-day activities of the organisation. These include:

- **The Portfolio Strategy and Management Board (PSMB)**, a dedicated portfolio governance committee consisting of members of the Leadership Team and other internal and technical subject matter experts. The PSMB provides expert advice and recommendations to the CEO on defining the target portfolio and managing its delivery. (See next section for more information on the process of Portfolio Management)
- **The Operations Committee (Ops Comm)**, a committee of the Leadership Team, has the objective and authority to manage operational aspects of the day-to-day internal business of CEPI.

Furthermore, CEPI has a leading role in the RDMIC, as part of the COVAX programme:

- **Research and Development and Manufacturing Investment Committee (RDMIC)**: managing funds under the Development and Manufacturing Workstream for COVAX, RDMIC is a multidisciplinary group with membership including the CEPI CEO, GAVI CEO, Bill and Melinda Gates Foundation President of Global Health and ex-industry experts, that manages the allocations of funds and provides investment decision recommendations to rapidly identify, develop and manufacture COVID-19 vaccines that can be deployed at scale to address global health needs

As the organisation grows under CEPI 2.0, the internal and external governance models are being reviewed to support the increased number of decisions required and CEPI's expansion into new technical areas. To address the increased size and value of CEPI's portfolio, robust oversight and risk management processes are being strengthened. To achieve the ambitions related to Connect, CEPI is investigating more creative use of its governance and advisory structures, including ensuring that CEPI has the appropriate delegations in place.

Portfolio Management

During CEPI 1.0, CEPI established core capabilities in portfolio management, risk management and R&D project management to actively monitor and manage its investments. These included i) a common portfolio management cycle for systematic project identification, selection, management and evaluation (Figure 7); ii) a dedicated portfolio governance committee—the PSMB—consisting of senior members of the CEPI leadership team and internal technical and subject matter experts); iii) standardised project and portfolio management practices to drive harmonisation and comparability across the portfolio; and iv) clear and consistent management and reporting of project and portfolio information.

CEPI's PSMB, with advice from the SAC and external experts, defines the target portfolio of vaccine candidate, platform technology and enabling sciences projects, and manages delivery of the portfolio according to a standard portfolio investment and management cycle (illustrated in Figure 7 above). The ultimate funding decisions are then made by the Board.

Figure 7: CEPI's Portfolio Management Cycle

In advance of entering into partnership agreements, CEPI performs financial, technical, and legal due diligence to ensure that development partners possess the necessary scientific, financial, and overall management expertise to advance products and manage significant sums of money. The partnership agreements also provide a mechanism for ensuring compliance with CEPI's equitable access policy.

CEPI manages projects through active engagement and routine monitoring and reviews. Approval criteria are applied to support periodic "stage-gate" reviews for partners seeking the next tranche of funding to advance to the next stage of development. A Joint Monitoring and Advisory Group (JMAG) consisting of key CEPI staff continually assess progress of individual projects, approve plans, and make recommendations to the PSMB concerning project continuation and the extension of additional funding through the formal stage-gate review process.

At the portfolio-management level, CEPI uses a range of analytical approaches as part of its annual strategic reviews to monitor risk and the value of the portfolio. Following close evaluation of the portfolio's progress, and of other unmet needs for vaccine R&D for EIDs, CEPI also plans for future additional investments. This is also informed by screening of new potential areas for funding, including analyses of vaccine research pipelines, calls for information, and new calls for proposals.

CEPI's approach to portfolio management was adapted and modified during the COVID-19 pandemic response to enable higher speed and greater flexibility in decision-making relating to COVID-19 portfolio investments. This included establishing a dedicated multidisciplinary R&D and Manufacturing Investment Committee (RDMIC) within the COVAX structure. The RDMIC is a multidisciplinary decision-making group, led by CEPI with industry expertise, that provides portfolio strategy and investment decision recommendations to rapidly identify, develop and manufacture COVID-19 vaccines that can be deployed at scale to address global health needs.

New COVID-19 project proposals and stage gate reviews of existing projects receive prior scientific and technical review through a dedicated Technical Review Group (TRG) and associated processes. The RDMIC then evaluates the recommendations emerging from such review in the context of the broader portfolio and the funds available for investment.

The overall portfolio governance framework is being reviewed as CEPI designs and implements CEPI 2.0 Operating Model, building upon portfolio governance experiences gained from CEPI 1.0 and COVID-19, and specifically incorporating findings from a PSMB effectiveness review conducted in Q4 2020, and an RDMIC effectiveness review conducted in Q2/Q3 2021.

To ensure effective portfolio governance is maintained during the transition of the core portfolio to CEPI 2.0, PSMB will continue to provide oversight of all aspects of the core portfolio investment decision-making and RDMIC will continue to oversee COVID-19 portfolio investment decisions. However, once the acute phase of the COVID-19 pandemic ends it is anticipated that longer-term governance for CEPI's COVID-19 R&D portfolio will revert to PSMB. Therefore, it will be important to ensure that the remit, composition and operating practices of CEPI's overall portfolio investment governance structure are reviewed and adapted as necessary in order to deliver effective overall portfolio oversight for CEPI 2.0.

Awardee Management

In July 2020 CEPI established a Project Management Office to implement clear project governance to ensure end-to-end project overview and support, establish project procedures and systematically monitor project performance.

The due diligence processes for CEPI consists of both technical, legal as well as financial/integrity due diligence. The technical due diligence reviews the integrated product development plan (iPDP), detailing how the candidate will be advanced. Issues of particular interest include research on humans (including management of human cells/tissues), animals, protection of personal data, environment, health and safety, research conducted in low- and middle-income countries, potential dual use or misuse of funding and any other ethics issues that might arise during the ethics evaluation. Legal due diligence looks at ensuring that the awardee can enter CEPI's funding agreement and conform to the various obligations and policies including appropriate access to relevant intellectual property and potential vaccine products and covering the ethical requirements referred to. Finally, integrity due diligence reviews whether a given entity is sanctioned, under embargo or are on a watch list, or on regulatory and law enforcement lists. Moreover, an assessment is made of whether there are political affiliations of concern (to Politically Exposed Persons or state-owned entities), adverse press/media or prior/ongoing litigation.

Each development programme is assigned a project team under the leadership of a Project Leader and Project Manager and supported by CEPI internal subject matter experts (pre-clinical, clinical, regulatory, chemistry/manufacturing, legal and other functions as appropriate), and finance. It is the responsibility of the project team to work closely with awardees, as defined in the project charter, to execute the project against the Integrated Product Development Plan using the project risk register to capture and mitigate risks, issue log to track actions and budgets. Project related issues and risks that may impact timelines, technical quality or financials identified by the project team are escalated and evaluated across CEPI governance bodies for guidance to minimise risk and accelerate project progression and to make the decision regarding any formal change requests received.

Performance Management

CEPI has developed a monitoring and evaluation (M&E) framework including performance management processes with the intent to support implementation of CEPI's strategy and programme document for the next business cycle (2022-2026). The objectives of the framework are to (i) measure the implementation of CEPI's strategy and programme document including the extent to which it has achieved its objectives, (ii) facilitate data driven decision-making by CEPI Management and Board, (iii) contribute to improvements of the CEPI model and learning for the vaccine development community more broadly. The M&E framework outlines three interlinked components of

- Routine monitoring of performance (e.g., through project and financial data)
- Evaluation against theory of change and KPIs (e.g., through reporting on key performance indicators as part of CEPI's Annual Progress Reports, independent evaluations)
- Dissemination and learning to promote a culture of learning and translating recommendations into actions

More information can be found in CEPI's Monitoring and Evaluation framework, which will be published on CEPI's website shortly.

Risk Management

Risk Management is engrained in CEPI's way of operating and seeks to identify, assess and manage the key risks to the organisation at all levels and in all of the activities undertaken to deliver on CEPI's targets. The continued growth of CEPI and the significant scale-up that the response to the COVID-19 outbreak has required, has undoubtedly resulted in significant change in the risk landscape for CEPI. Supported by a strong culture of taking risks into account in planning activities and decision-making, CEPI has been able to attract a substantial amount of funding, grow the organisation, adapt the ways of working, and identify and develop a vaccine R&D portfolio towards a rapid response to the COVID-19 outbreak. This took place in parallel with managing and making progress developing CEPI's core portfolio of priority pathogens and other pre-COVID- 19 activities.

As CEPI grows and becomes a more complex operation, the approach to manage risks evolves. Thus, CEPI has gradually improved and established new processes to stay abreast of changes. The strategic shift CEPI 2.0 represents will require a thorough assessment of what changes CEPI will be facing and identification of the risks accompanying the required transformation. This section provides an introduction to the risk management approach in CEPI, the risks associated with the implementation of CEPI 2.0 and the organisation risks CEPI is likely to face in the strategic period.

Risk Management Approach

CEPI's approach to risk management is set forth in a risk management policy, which includes procedures with guiding principles and a description of the process for risk management. Recognising that all activities involve a certain amount of risk, CEPI does not aim to avoid all risks, but rather to make informed decisions that support achieving strategic objectives. Effective risk management will protect CEPI assets and people, while helping to ensure both CEPI and its partners comply with applicable laws and regulations. CEPI's approach to risk management is to deliver benefits for an appropriate level of effort. The operating principle is that risk management should be integrated in daily ways of working.

CEPI manages and monitor risks on three levels:

- **Organisational level** – organisationally risks are monitored across 5 categories: Strategic, Programme, Finance, Operational and Legal/ Compliance. Key risks are reviewed by Risk Owners through a quarterly review of departmental priorities, budgets and risks, followed by CEPI Leadership Team review. In CEPI's Risk Management framework, The CEPI Board, the Audit and Risk Committee, the CEO, the Risk Owners, and the Head of Governance Risk and Compliance have defined roles in carrying out the monitoring and governance associated with the management of risks.
- **Investment portfolio level** – Risks associated with CEPI's core operation of being a funder are monitored and managed by the CEPI Portfolio Strategy and Management Board. Key portfolio risks feed into organisational top risks.
- **Project level** - Partners granted funding from CEPI are obliged to identify key risks to their projects. These risks are monitored by both CEPI's project management team and the Joint Monitoring and Advisory Group that is established for an individual project. Risks and mitigating measures are part of each milestone review. Following a due diligence process, CEPI also maintains internal risk registers to monitor project and partner risks; all are subject to regular review and are included in reporting at the portfolio management level.

Moreover, annual audits of CEPI accounts are conducted by an external auditor appointed by the Board. These audits are conducted as directed by the International Standards on Auditing (ISA). CEPI is in addition obtaining further assurance related to risk management through its internal audit work as detailed in an Annual Internal Audit Plan. The activities carried out in connection with the Annual Internal Audit Plan comprise of both internal facing, as well as partner facing, activities to obtain assurance that risk mitigation activities are effectively implemented and operating.

CEPI 2.0 Implementation - Strategy Execution Risk

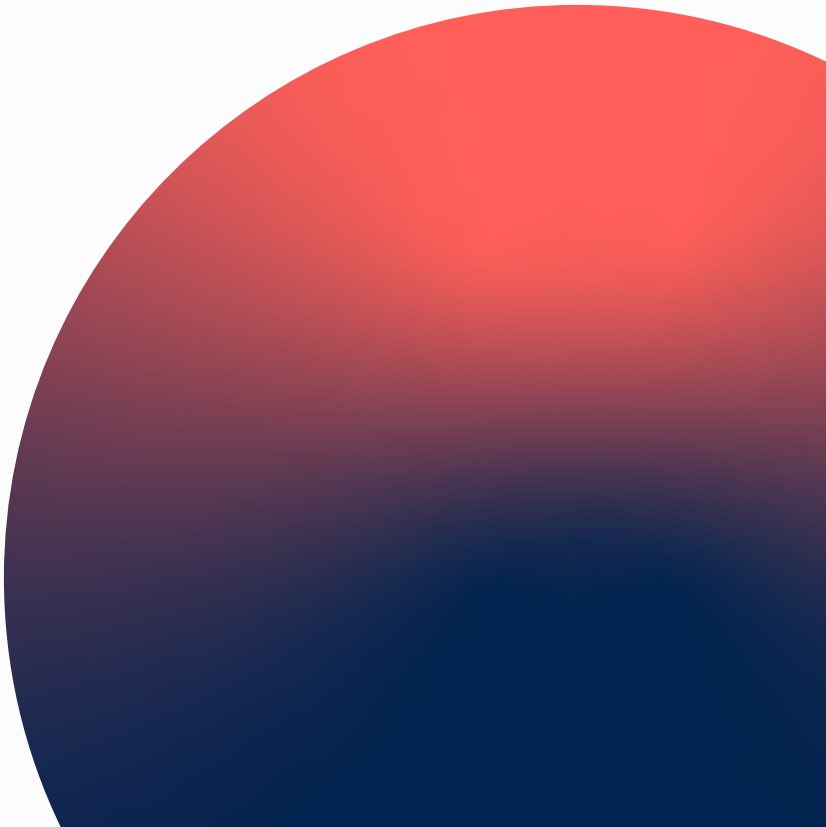
Following the development of the CEPI 2.0 strategy there is the need to address the ability to implement a new strategy, the strategy execution risk. More specifically, there is a risk of mismatch between what CEPI 2.0 was designed to accomplish and the approach to implement it. Four key strategy execution risks are:

- Risk of not adequately translating CEPI 2.0 from high-level ambitions to specific actions the organisation must take to make that ambition a reality
- Failure to put in place the organisational capabilities required to sustain the strategy after it is enacted
- Failure to appropriately adapt the strategy when conditions change
- Risk of not mobilising the funding needed to deliver planned activities

To reduce the risk of unsuccessful implementation, CEPI established a cross-functional programme to ensure aligned planning, preparation and implementation of activities related to 2.0. The CEPI 2.0 Implementation Office coordinates and drives the programme, with support from cross-cutting workstreams and technical working groups. The progress of the implementation programme is overseen by CEPI Leadership Team.

The objectives of the implementation programme are to:

- Define 2022-2026 strategy roadmaps ("what CEPI will deliver"), detailing organisation activities and the phasing of these
- Engage as part of the global health ecosystem to define and implement CEPI's role (and the role of others) in an effective global preparedness and response architecture
- Define CEPI's future resource and capability needs to deliver 2.0, and adapt CEPI's operating model to support growth
- Develop an integrated and cohesive results framework (theory of change and key performance indicators) to communicate a compelling value proposition to investors, and as a basis for monitoring and evaluating performance
- Align with and support resource mobilisation efforts
- Drive consistent communication and alignment around CEPI 2.0.



How will CEPI 2.0 change the risks the organisation faces

CEPI 2.0 sets out ambitious goals, with an expanded mandate, and a new role at the centre of a global health ecosystem which is facing major challenges amidst a global pandemic. The strategic shift for CEPI is building on and evolving the current objectives and capabilities of the organisation, but there are also objectives that are new. The financial forecast for the new strategy implies a significant growth resource mobilisation, which also means the organisation will manage a substantial increase in the amount of funds accompanied by increased attention and scrutiny.

From an organisational risk perspective, this will require more resources from CEPI to manage the existing key risks. However, new risks will also surface as a result of CEPI's new and a more prominent role, as well as the new activities CEPI plans to launch. Management will conduct reflective exercises to understand key perceived risks through CEPI 1.0, unanticipated risks/issues, effectiveness of mitigation activities, and draw lessons learned from that experience. Reflecting in such a holistic way will help evolve how CEPI considers and conducts risk management, as well as how it identifies risks. CEPI's Governance Risk and Compliance function maintains an assessment of CEPI's top risks relating to the 2.0 Strategy (see Annex 3 - Risk Register), including the following aspects:

- Resource mobilisation
  - The prerequisite for attracting major and sustainable funding to enable planned activities.
  - Complexities in raising short- and long-term funding in an environment where nation states and other funding institutions grapple with the prioritisation of funds to tackle global health emergencies, including issues of self-sufficiency vs. multilateral efforts through actors such as CEPI.
- Partnership and ecosystem
  - The dependency on partners will increase and require more and well-structured management— upstream and downstream.
  - The need for alignment in the global health ecosystem will evolve and be a key enabler for achieving equitable access in larger scale outbreaks.
- Prominence and scrutiny
  - Expectations are higher and there is less room for failure; CEPI's role and objectives must be well communicated.
  - Hackers have targeted the healthcare industry during COVID-19 pandemic and will continue to do so, putting CEPI and other health organisations at risk of being a target for those with harmful intentions.
  - The new strategic period brings significant financial resources for CEPI to manage appropriately.
- Programme management and operation execution
  - CEPI is setting up a larger operation with a significant increase in overall portfolio size as well as the number of partners and projects funded. The need for robust processes and capabilities to attract, select, manage and monitor grant recipients and projects, and to manage the overall portfolio of investments will increase.
  - The number of activities planned under 2.0 will require the organisation to balance and prioritise the individual investment programmes with the funds mobilised.
  - Potential areas of expansion under discussion (therapeutics and manufacturing), but also technological tools and digitalisation (artificial intelligence/machine learning/outbreak surveillance) require new capabilities.
  - Establishing the right operating model for CEPI to manage the new scope of activities.

Financial Forecast 2022-2026

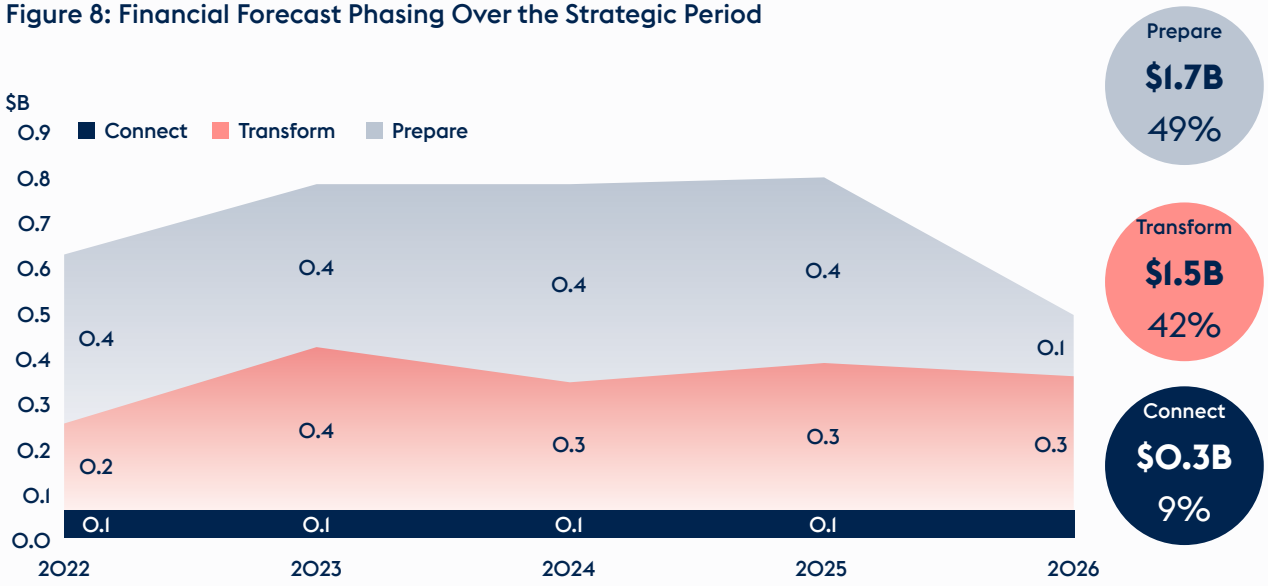
The table below describes the total funding needed for CEPI to achieve the outcomes set out in the strategy: US$1.7 billion to Prepare, US$1.5 billion to Transform and US$0.3 billion to Connect, in total US$3.5 billion[32].

Table 2: Funding Need per Strategic Outcome*

Strategic objective	Outcome	Total ($B)
Prepare	Outcome 1.1: Accute phase of the Covid-19 pandemic ended	0.7
Prepare	Outcome 1.2: Development of vaccines and other biological countermeasure against known high-risk pathogens accelerated	0.8
Prepare	Outcome 1.3: Risk of further coronavirus pandemics reduced	0.2
	Prepare	1.7
Transform	Outcome 2.1: Vaccine prototype and platform innovations used to give a head-start on novel threats	1.0
Transform	Outcome 2.2: Enabling sciences scaled to further accelerate vaccine development	0.4
Transform	Outcome 2.3: Vaccine manufacturing transformed	0.1
	Transform	1.5
Connect	Outcome 3.1: Financing for epidemic preparedness and response secured	0.0
Connect	Outcome 3.2: Coordination among key stakeholders enables system readiness	0.1
Connect	Outcome 3.3: Equitable access principles as the foundation of any effective global response	0.2
	Connect	0.3
	Total CEPI 2.0 Funding need	3.5

*These estimates are preliminary and subject to change.

Figure 8: Financial Forecast Phasing Over the Strategic Period



[32] The financials building up to the US$3.5 billion CEPI 2.0 investment case have been validated and updated as part of the work with the CEPI 2.0 Programme document. Figures might therefore vary compared to the investment case published early 2021.

- Early 2021 CEPI also published an ask for COVID-19 funds as a frontload against the US$3.5 billion CEPI 2.0 investment case. US$220 million against this ask has been secured, thus reducing the actual funding need to US$3.3 billion.
- Apart from US$220 million in pledges received in 2021, the funding need presented takes into consideration CEPI's financial position at the start of the 5-year cycle.
- Funding need for COVID-19 might come down as investments structured as forgivable loans are secured and available for reinvestments.

Abbreviations

CDC	Centre for Disease Control
CEPI	Coalition for Epidemic Preparedness Innovations
CEPINET	Community engagement practitioner network
COVAX	COVID-19 Vaccines Global Access
COVAX AMC	COVID-19 Vaccines Global Access Advanced Market Commitment
DCVMN	Developing Countries Vaccine Manufactures Network
EFPIA	European Federation of Pharmaceutical Industries and Associations
EID	Emerging Infectious Diseases
EVD	Ebola Virus Disease
Gavi	Gavi, the Vaccine Alliance
GCLP training	Good Clinical Laboratory Practice Training
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
HIC	High Income Country
HLIP	High Level Independent Panel
ICMRA	International Coalition of Medicines Regulatory Authorities
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IVI	International Vaccine Institute
IPPR	Independent Panel for Pandemic Preparedness and Response
KPI	Key Performance Indicator
LIC	Low Income Country
LMIC	Low- And Middle-Income Country
MERS	Middle East respiratory syndrome
mRNA	Messenger Ribonucleic Acid
NC3Rs	National Centre for the Replacement, Refinement and Reduction of Animals in Research
NIBSC	National Institute for Biological Standards and Control
ODA	Official Development Assistance
PAHO	Pan American Health Organization
PHE	Public Health Emergency
PPP	Pandemic Preparedness Partnership
RNA	Ribonucleic acid
R&D	Research and Development
RVF	Rift Valley Fever
SARS	Severe Acute Respiratory Syndrome
TPP	Target Product Profile
UMIC	Upper Middle-Income Country
UNICEF	United Nations Children's Fund
WHO	World Health Organization
WHO EUL	WHO Emergency Use Listing
WTO	World Trade Organization

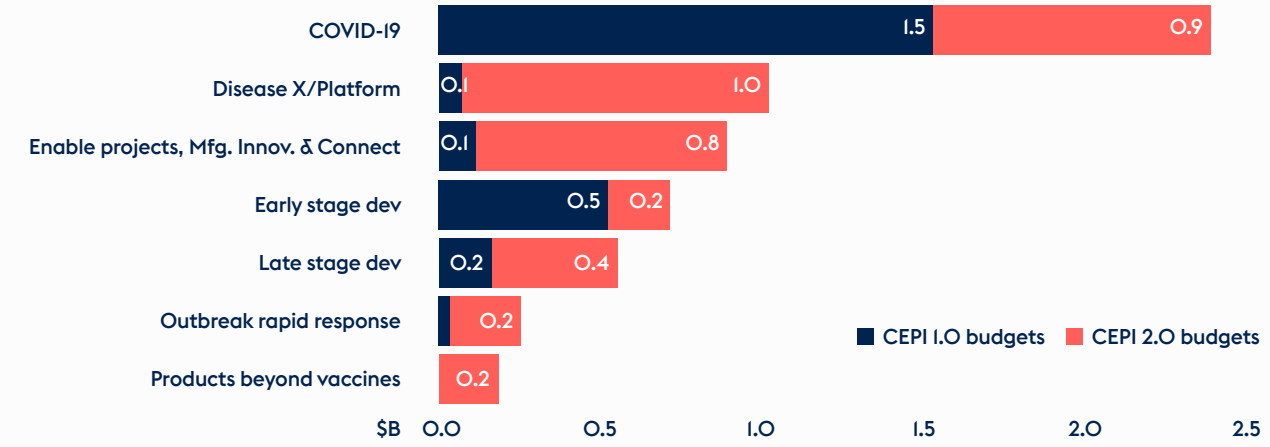
Annex 1-3

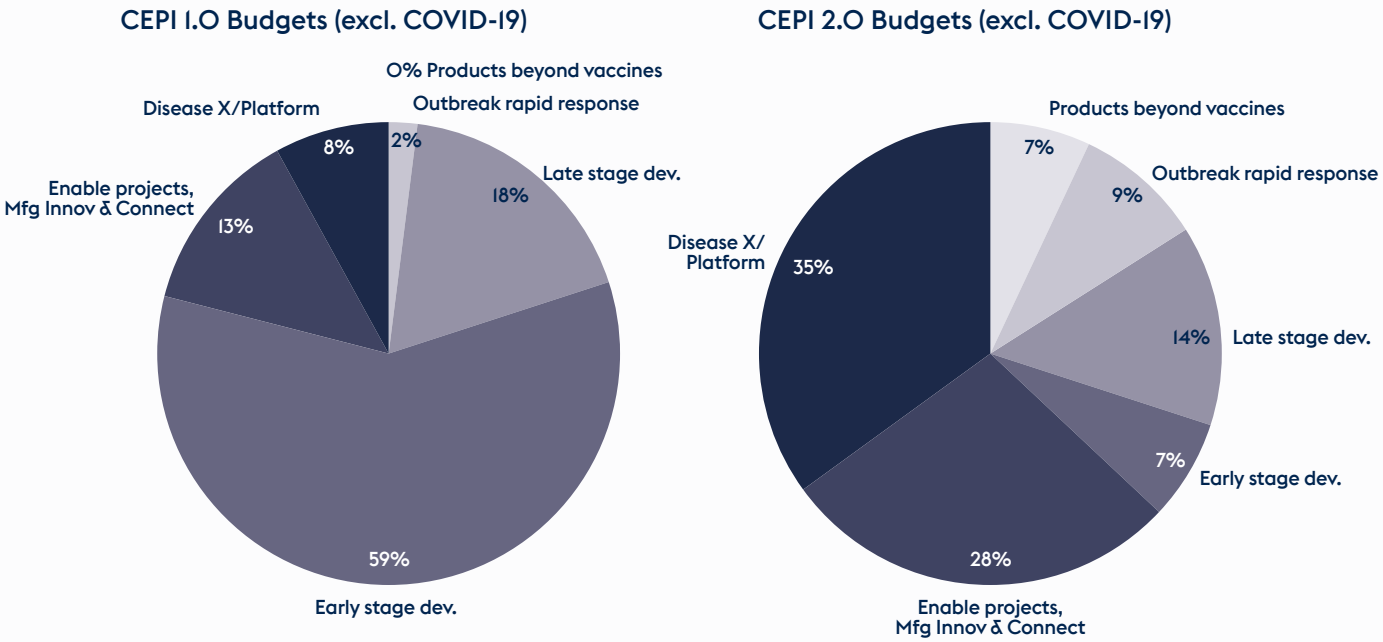
ANNEX 1 – Technical and Financial Evolution: From CEPI 1.0 to CEPI 2.0

CEPI's strategy for 2022-2026 carries forward a technical and financial evolution from CEPI 1.0. The resources required for the strategic ambitions under 2.0 reflect an expanded scope, building on lessons learned from CEPI 1.0 and from the COVID-19 pandemic response. Concretely, this includes:

- Continuation of vaccine development of priority pathogens beyond late stage (Phase 2b/3) towards licensure for priority pathogens with a clear unmet need where vaccines could have an impact.
- Modest investments in products beyond vaccines by initiating the development of a monoclonal antibody programme focusing on certain parameters—driving down costs and making these technologies accessible to all, with the aim of two priority pathogen prophylactic monoclonal antibodies ready for emergency use.
- Expanded focus on Disease X—an outbreak caused by a pathogen currently unknown to cause human disease—by harnessing innovations in vaccine development and manufacturing, including investments in virus family vaccine libraries, prototypic approach and innovations that can 'transform' manufacturing cheaper, faster and closer to an outbreak.
- Elevating CEPI's role in connecting with other stakeholders in the ecosystem to enable rapid countermeasure development, effective response and equitable access for those in need, which will include discussions with partners to articulate the configuration of a 'target ecosystem profile', investing and supporting networks of ready-to-act entities across a set of core functional areas (e.g., Enabling sciences), and promoting sustainable diversified manufacturing for CEPI-funded programmes.

Figure 9: From CEPI 1.0 to CEPI 2.0 | Technical and Financial Evolution[33]



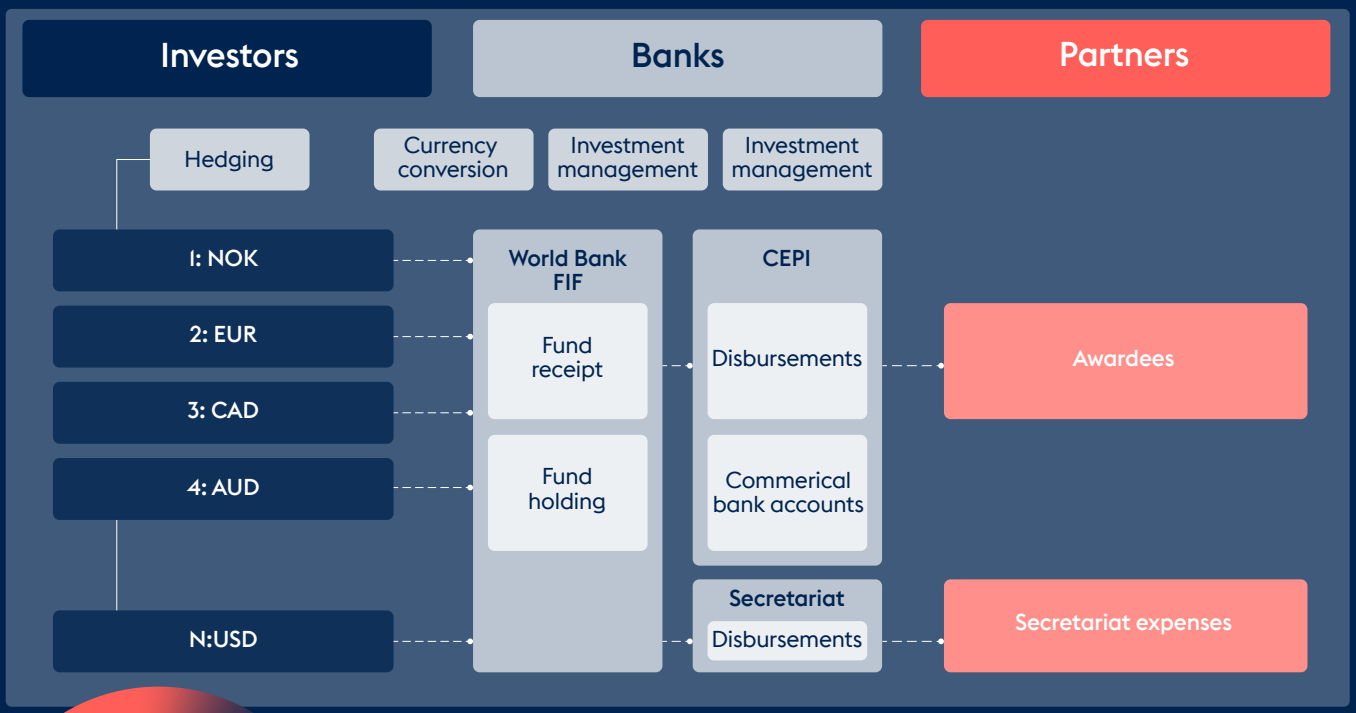


[33] Total budget for CEPI 2.0 is US$3.6 billion. This is higher than the funding need due to a positive net financial position for CEPI 1.0 (incl. COVID-19 and already secured repayments of forgivable loans).

ANNEX 2 – Fundholder Arrangements

The World Bank is CEPI's principal fundholder, and the Norwegian bank DNB is CEPI's operational banking partner. As depicted in Figure 10 below, these arrangements serve to facilitate the financial flows between Investors and Partners, with CEPI as the intermediary.

Figure IO: CEPI flows and financing



Starting from the left, CEPI will receive funds from investors in a multitude of currencies. To mitigate risks of fluctuations, CEPI is constantly reviewing the currency exposure to avoid negative impacts on its budget, which is denominated in US$. The World Bank is the fundholder of CEPI funds through a Financial Intermediary Fund (FIF). The FIF will hold funds for as long as deemed necessary by CEPI and disburse funds to commercial bank accounts upon request by the CEPI Finance team. Subsequently, funds will be transferred from the commercial bank accounts to awardees of CEPI investment projects according to individual project plans. CEPI also holds separate bank accounts in USD, NOK, GBP, and EUR for operational expenses incurred in either of the CEPI offices.
Both the FIF and the commercial bank accounts will invest the positive balance at any given point in time within the frame of CEPI's Investment and Treasury policy and procedure. Hedging of currencies will take place in commercial banks (based on the Hedging policy) and supplemented by spot conversions in the commercial bank or in the FIF as needed (dependent on to which bank the donor chose to transfer their contribution).

Table 3: Overview of Services Provided by the World Bank and Commercial Banks Respectively

Services	World Bank	Commercial banks
Hedging		✓
Investment management	✓	✓
Short term credit		✓
Currency conversion	✓	✓
Fundholding	✓	✓
Operating bank accounts (NO/UK/US(CH))		✓
Awardee disbursements		✓

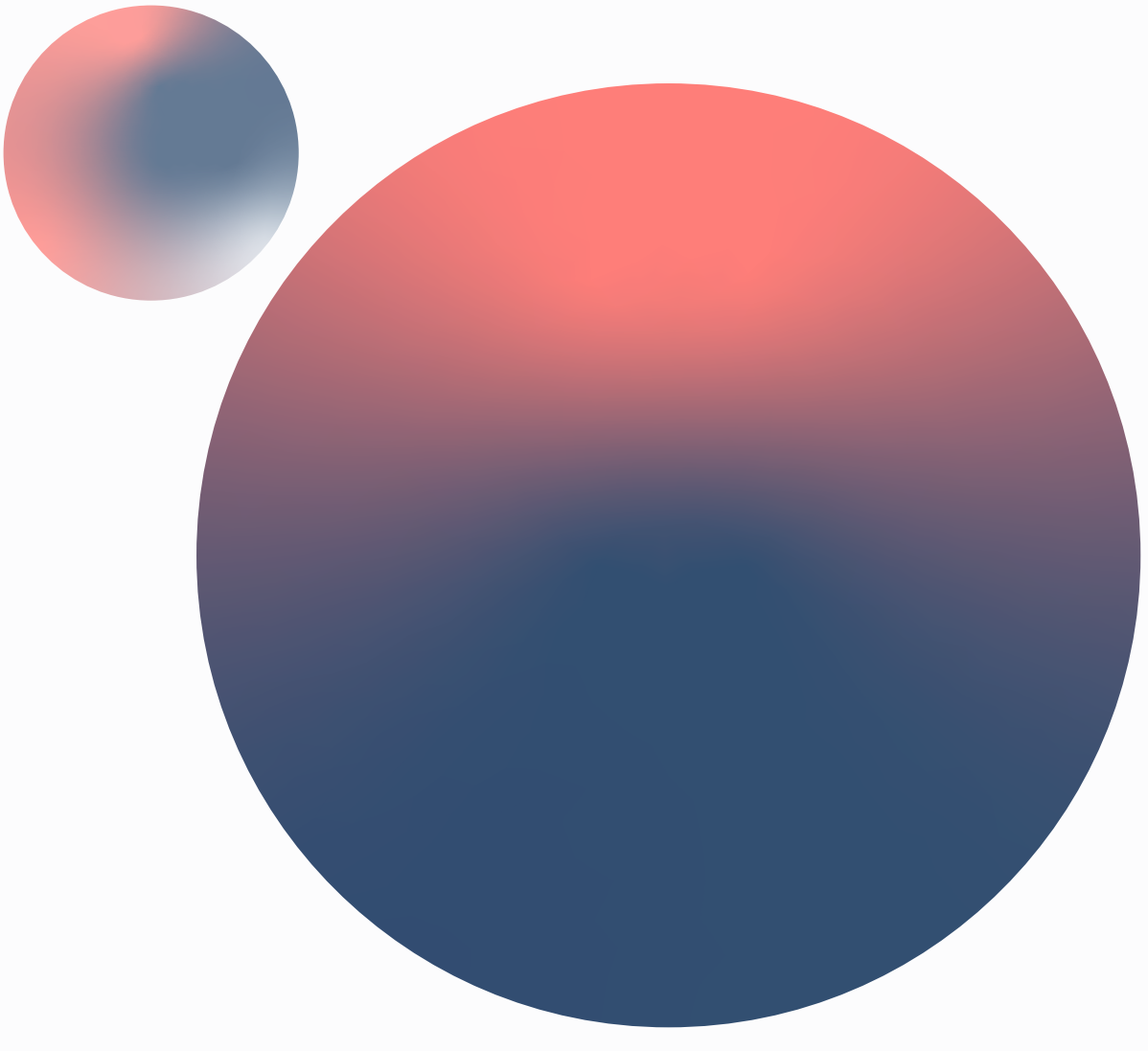
ANNEX 3 – Risk Register

Strategic risks

- **Mandate scope:** Lack of clarity around CEPI's role in outbreak response vs. ongoing development, upstream vs. downstream
- **Mission execution:** Inability to fulfil equitable access commitment, shortage of necessary vaccines, especially in LMICs, and CEPI perceived as responsible
- **Alternative solutions:** Questions around CEPI's value-add if therapeutic alternatives become available (non-CEPI or other therapeutic modalities)
- **Limited impact of vaccine:** Questions around CEPI's value-add based on doubts around vaccine relevance (mild outbreak/delivery too late)
- **Risk tolerance / flexibility:** Questions around CEPI's ability to strike the right balance between risk tolerance and flexibility in outbreak mode
- **Funding risk:** Lack of timely and sufficient funding for CEPI to meet investment targets, slower progress and/or less priority activities launched
- **Ecosystem relevance risk:** Global/regional/national funding sources prioritize alternatives to CEPI, inc. manufacturing perceived as more important than R&D, or CEPI not being able to differentiate itself from R&D&M work of others
- **Dynamic ecosystem:** Competition, unpredictability, and lack of clarity and alignment within ecosystem impacts CEPI's ability to reach its goals
- **Timeliness and transparency:** Ability to deliver not corresponding to audience' expectations in terms of timeliness and transparency
- **Expectation setting:** Long term negative effect of not meeting expectations that could be unrealistically high
- **CEPI 2.0 implementation:** mismatch between what CEPI 2.0 was designed to accomplish and the approach to implement it, specifically:
  - Risk of not adequately translating CEPI 2.0 from high-level ambitions to specific actions the organization must take to make that ambition
    a reality
  - Failure to put in place the organizational capabilities required to sustain the strategy after it is enacted
  - Failure to appropriately adapt the strategy when conditions change
  - Risk of not mobilizing the funding needed to deliver planned activities

Programme risks

- Portfolio size: Insufficient number of projects / scale of investments to deliver the target number of vaccine candidates
- Portfolio composition: Inappropriate portfolio composition to achieve target number of vaccine candidates, specifically:
  - Narrow range of (unvalidated) technology platforms present increased risk of late-stage attrition (efficacy, safety and/or scale up)
  - Narrow range of (smaller/inexperienced) vaccine developers present increased risk of attrition (efficacy, safety and/or scale up) and/or delays
  - Narrow geographic distribution of developers / manufacturers presents increased risk to achieve broad access
- Negative impact on broader CEPI Portfolio: Focus on outbreak response projects/portfolio diverts attention/ resource from broader portfolio
- Information deficiency: Lack of correct or sufficient information as basis for decision-making (e.g. epidemiological)



Operational risks

- **Operational inefficiency:** CEPI's operations become inefficient due to:
  - lack of appropriate tools and techniques to help staff perform their work
  - lack of clarity on roles and responsibilities inside the organisation; duplication of roles and / or lack of ownership for key processes
  - lack of necessary training assets to help staff perform their work
  - unclear priorities and misalignment between departments and functions
- **CEPI capacity:** Operational limitations with regards to managing large number of complex projects simultaneously in case of outbreak
- **Staff capacity:** Staff fatigue, exhaustion, or loss of staff or loss of morale at the end of the pandemic when CEPI returns towards "business as usual"
- **Decision-making quality:** Lack of objective decision-making internally, risk of overconfidence, specifically inability to make effective portfolio entry and / or progression decisions
- **Candidate quality and actions:** Limited ability to verify grant recipient's compliance with regulatory / manufacturing stipulations
- **CEPI legal / process compliance:** Balance between need to accelerate and be creative / fast while still following due process
- **New types of partnerships:** Questions around appropriate checks and balances, capabilities in contract and partner management
- **Relationship with MNCs and key developers:** Questions around the issues related to close collaboration with MNCs, inc. that developers struggle with CEPI EA provisions, and reduced willingness from developers to invest in the future as result of discontinuation of investments
- **Relationships with other outbreak response partners:** inefficient alignment with partners, and reliance on others or developing multiple relationships upon which CEPI's success is dependent, increasing the opportunities for challenges from externalities beyond CEPI's control
- **Security and organisational resilience:** cyber and security incidents or crisis situations putting risk to staff safety, financial loss, disruption, damage to the reputation of CEPI and data integrity

Financial risks

- **Budget constraints:** Financial limitations with regards to managing several complex projects simultaneously in case of outbreak
- **Financial decisions:** Poor management of resources and increased potential for "wrong" investment
- **Investment expansion:** Pressure to expand investment beyond CEPI scope, ability and/or capacity
- **Fraud and financial mismanagement:** Fraud, misconduct and mismanagement of CEPI funds (majority public funds)
- **Financial reporting:** Risk associated with CEPI Financial Statements not being approved, lack of compliance with investor requirements

Legal/compliance risks

- **Investor requirements:** non-compliance with investor specific requirements damaging investor relationships, risking funds to be clawed back
- **Abuse of power:** Fraud, misconduct and mismanagement of funds pose a great threat to CEPI's reputation and could lead to investors pulling out of the coalition, partners not willing to cooperate or a general lack of trust that could lead to CEPI losing its current position as a global health security actor.
- **Conflicts of interest:** Lack of integrity and objectivity in decision-making and representation
- **Corruption:** Corruption in funding arrangements and payments, internal and external
- **ODA eligibility:** investments not being (fully) ODA eligible leading to potential funding constraints for investors/CEPI
- **Ethics:** CEPI and partners failure to adhere to appropriate ethical, cultural and social norms, including human rights

* List of key risks to CEPI in 2.0; the ones highlighted are those seen as CEPI's "top" risks

CEPI