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# Funding the development and manufacturing of COVID-19 vaccines

Background paper for the World Bank/CEPI financing COVID-19 vaccine development consultation on February 20, 2020

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The authors have updated the paper to reflect the current status of the COVID-19 pandemic and efforts to develop a vaccine.

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## STRUCTURE OF THIS PAPER

This paper is organized into eight sections. **Section 1** makes the case for why we urgently need a COVID-19 vaccine. **Section 2** argues that new funding for COVID-19 vaccine development is required for all development stages and gives estimates of how much funding is needed. **Section 3** examines ways to mobilize such funding. **Section 4** explores potential funding vehicles. It makes the case that CEPI is well placed to be the vehicle for funding pre-clinical development, clinical development, and “scale out,” but that a different vehicle would be needed for funding manufacturing and delivery. **Section 5** discusses governance of a CEPI funding window for development of COVID-19 vaccines. **Section 6** highlights vaccine manufacturing, intellectual property (IP), global access, and regulatory approval, and **Section 7** highlights issues (including ethical considerations) in conducting trials in the midst of the COVID-19 outbreak. **Section 8** briefly summarizes our main conclusions.

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## TABLE OF CONTENTS

Acronyms .....	3
Executive summary .....	4
<b>1</b> Introduction: the urgent need to develop and manufacture COVID-19 vaccines.....	7
<b>2</b> Why funding is needed for the development of COVID-19 vaccines .....	10
<b>3</b> Mobilizing an additional US\$2 billion for COVID-19 vaccine development and deployment.....	14
<b>4</b> CEPI as a venue for funding late stage development of COVID-19 vaccines .....	16
<b>5</b> Governance of new COVID-19 vaccine funding channeled through CEPI .....	19
<b>6</b> Addressing challenges in manufacturing, intellectual property, access, and regulatory approval .....	20
<b>7</b> Conducting late stage trials in the midst of the outbreak .....	23
<b>8</b> Conclusions .....	26

## BOXES

<b>Box 1.</b> About CEPI .....	17
<b>Box 2.</b> CEPI's equitable access policy.....	21
<b>Box 3.</b> Conducting trials during outbreaks: what can we learn from the 2014-2016 Ebola epidemic in West Africa?.....	23
<b>Box 4.</b> Nuffield Council of Bioethics' Call for Action on the ethical conduct of health research in emergencies .....	25

## TABLES

<b>Table 1.</b> The six COVID-19 candidate vaccines funded by CEPI as of March 17, 2020.....	12
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## FIGURES

<b>Figure 1.</b> Schematic of a funding approach to COVID-19 vaccine development .....	5
<b>Figure 2.</b> Stages of vaccine development and delivery.....	11

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## ● ACRONYMS

<b>AMC</b>	Advanced Market Commitment
<b>APC</b>	Advanced Purchase Commitment
<b>BMGF</b>	Bill & Melinda Gates Foundation
<b>CEPI</b>	Coalition for Epidemic Preparedness Innovations
<b>CFR</b>	Case Fatality Rate
<b>CREDO</b>	Clinical Research During Outbreaks
<b>DCVMs</b>	Developing Country Vaccine Manufacturers
<b>EIDs</b>	Emerging Infectious Diseases
<b>EMA</b>	European Medicines Agency
<b>FDA</b>	United States Food and Drug Administration
<b>FIF</b>	Financial Intermediary Fund
<b>GMP</b>	Good Manufacturing Practice
<b>GSK</b>	GlaxoSmithKline
<b>IAVI</b>	International AIDS Vaccine Initiative
<b>IFFIm</b>	International Finance Facility for Immunisation
<b>IP</b>	Intellectual Property
<b>IVI</b>	International Vaccine Institute
<b>MCM</b>	Medical Countermeasure
<b>MICs</b>	Middle-income Countries
<b>MNC</b>	Multinational Company
<b>NOK</b>	Norwegian Krone
<b>NRAs</b>	National Regulatory Authorities
<b>ODA</b>	Official Development Assistance
<b>ODI</b>	Overseas Development Institute
<b>PATH</b>	Program for Appropriate Technology in Health
<b>PEF</b>	Pandemic Emergency Financing Facility
<b>PHEIC</b>	Public Health Emergency of International Concern
<b>R<sub>0</sub></b>	Basic Reproductive Number
<b>SAC</b>	Scientific Advisory Committee
<b>SARS</b>	Severe Acute Respiratory Syndrome
<b>UNICEF</b>	United Nations Children's Fund
<b>WHO</b>	World Health Organization

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## ● EXECUTIVE SUMMARY

### Why do we need a vaccine?

The virus that causes COVID-19, the SARS-CoV-2 virus, has quickly spread worldwide. On January 30, 2020, the WHO declared COVID-19 to be a Public Health Emergency of International Concern (PHEIC) and advised all governments to prepare for transmission in their countries. On March 11, 2020, the WHO declared that it had become a pandemic. There is uncertainty about what will happen next, e.g., the pandemic could involve multiple waves (i.e., simultaneous epidemics) of COVID-19 over 1-3 years, and/or SARS-CoV-2 could become a globally endemic virus. We need to prepare for a worst-case scenario, in which the rapid development and scale-up of COVID-19 vaccines is critical to reducing the morbidity, mortality, and economic damage associated with a pandemic. Were SARS-CoV-2 to become endemic, any vaccines developed would likely find sustained global demand for their production.

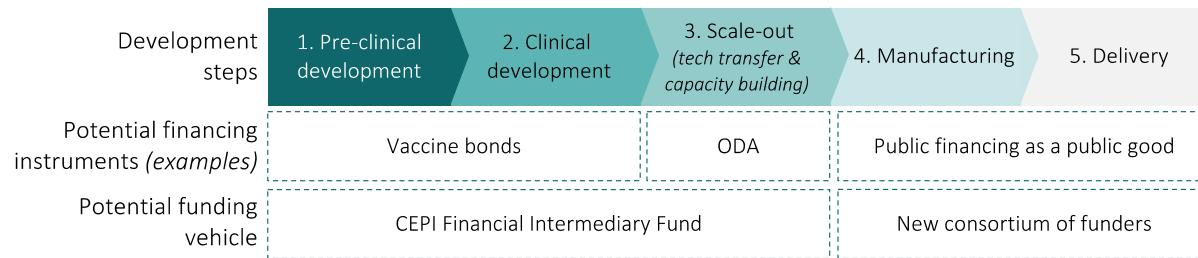
### How much funding do we need and what are the core goals of this funding push?

CEPI has proposed three core goals for its vaccine development efforts—**speed**, **scale**, and **access**—goals that will entail large investments in a short time horizon and a high tolerance for risk. CEPI estimates that the costs of developing one or more vaccines, inclusive of clinical and process development with scale-up and potential transfer of manufacturing, are likely to be in the range of US\$2 billion. It must be noted that these costs are much lower than the costs of inaction—the economic costs of COVID-19 in China alone are estimated to be US\$62 billion in the first quarter of 2020. These cost estimates presume development to the point at which the vaccines can be licensed or used under emergency use provisions and *do not include* costs for subsequent manufacturing, delivery, or administration.

While the urgent need is to develop COVID-19 vaccines, this crisis could potentially also be an opportunity to begin developing a sustained mechanism to mobilize new financing for development and product manufacturing for a broad range of emerging infectious diseases (EIDs) and neglected diseases.

### How could the funding gap for COVID-19 vaccine development and deployment be closed?

Closing the US\$2 billion funding gap will require contributions from the public, philanthropic, and private sectors. All countries are at risk, and must be prepared, which means there is a strong case for all governments to invest in COVID-19 vaccine development and deployment as part of their health systems preparedness investments. There is also an opportunity to use innovative finance mechanisms, such as vaccine bonds and advanced market commitments, and instruments within the World Bank's health portfolio, such as contingent emergency response components. It may be valuable to match different types of financing instruments with different steps in the vaccine development and deployment process (Figure 1). For example, vaccine bonds could be used to finance clinical and process development; official development assistance (ODA) could fund tech transfer from multinational companies to manufacturers in middle-income countries (MICs), including capacity building; public funds could be used to procure vaccines as a global public good (GPG).



**Figure 1. Schematic of a funding approach to COVID-19 vaccine development (pandemic with multiple waves of COVID-19 over 1-3 years)**

### Why would CEPI be an appropriate venue for a new financing window for the development of COVID-19 vaccines?

If provided with sufficient resources, CEPI is an existing platform with scientific expertise and networks that could be leveraged to support and oversee the first three steps in the COVID-19 vaccine development process: pre-clinical development, clinical development, and “scale out” (i.e. tech transfer and capacity building in MICs). It would not be the right vehicle for funding manufacturing of vaccine for general use or its delivery, which are outside CEPI’s remit (Figure 1). CEPI funds the development of vaccines against a range of WHO’s Blueprint priority pathogens. By using an existing platform as the “add-on” venue for funding advanced development of COVID-19 vaccines, transaction costs would be lower than launching a new mechanism. Using CEPI as the platform would mitigate concerns about fragmentation and “cannibalization” of R&D funding for EIDs/neglected diseases. Additional expertise on funding phase III trials and in tech transfer through CEPI could be quickly incorporated without large investments. Once this expertise and funding window for late stage development is in place, the window would be “ready to go” for future outbreaks. Even if the COVID-19 outbreak wanes, opening this new window at CEPI will help to sustain attention to the importance of epidemic vaccine development. CEPI’s existing equitable access policy appears to be flexible enough to apply to the expansion of CEPI-funded activities to phase III trials and beyond. Similarly, CEPI’s existing governance arrangements have flexibility to adapt to the expanded scope of work contemplated by this new financing window. CEPI is already supported by a World Bank financial intermediary fund (FIF), and so using this existing FIF to finance development of COVID-19 vaccines would allow for speed, low transaction costs, flexibility, and global access.

### How would manufacturing and delivery of COVID-19 vaccines be funded?

The fourth and fifth steps in the COV-19 vaccine development process—manufacturing and delivery—would require a separate financing mechanism outside of CEPI. A consortium of public and philanthropic funders is likely to be needed.

### How would the manufacturing challenges be addressed?

For COVID-19 vaccines under development through CEPI funding, none of the current partners has experience in bulk manufacturing and they have not previously licensed a vaccine. CEPI is in the process of reviewing additional proposals and anticipates expanding its portfolio with additional vaccine candidates, and it is hoped

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that some of these will be sponsored by experienced manufacturers. For manufacturing at scale, it is likely that a consortium of manufacturers—including multinational companies (MNCs), contract manufacturing organizations (CMOs), and developing country vaccine manufacturers (DCVMs)—will be needed to produce the large numbers of doses that may be required (e.g., a billion doses 12-18 months from now). A new public-private partnership model for bulk manufacturing of COVID-19 vaccines by such a consortium of manufacturers is likely to be needed.

### **How would regulatory challenges be addressed?**

Regulatory agencies and bodies, including the WHO, the US Food and Drug Administration, the European Medicines Agency, and the International Coalition of Medicines Regulatory Authorities, recognize the urgency of providing a simplified and expedited, joint regulatory review of COVID-19 medical countermeasures (MCMs). There is widespread recognition that a “business as usual” approach is not tenable given the speed at which a pandemic may spread.

### **How would global access to COVID-19 vaccines be ensured?**

Affordability and accessibility must be the bedrock of any proposal for a new funding push for COVID-19 vaccine development. The poor are hit “first and worst” by outbreaks, and any access model that ends up giving only high-income countries access to the vaccine would clearly be unacceptable. It will be critical to avoid a scenario in which high-income country governments enter into bilateral purchase contracts with manufacturers, thus monopolizing the vaccine. In the current pandemic scenario, which may involve multiple waves of COVID-19 over many years, one global access model would be for the vaccine to be procured with public funding and allocated as close to pro rata as possible to countries. In this pro rata scenario, countries would probably need some additional way to prioritize who receives the vaccine (e.g. giving it first to health workers and the medically vulnerable). The consortium of manufacturers discussed earlier (MNCs, CMOs, and DCVMs) would ideally provide a “cost plus” contract (with a small margin) for sales to a global purchasing agent for a time-limited period; the vaccine would then be free at the point of care. If COVID-19 then becomes a globally endemic pathogen, successful vaccines could transition to commercial sales and a tiered pricing model could be adopted.

### **How can we ensure that a COVID-19 vaccine funding push does not siphon off funding needed for other global health priorities?**

Additional funding is clearly needed for development and deployment of COVID-19 vaccines, but this effort should be complementary to other fund-raising processes (e.g., WHO’s mobilization of resources for pandemic response and preparedness as well as the upcoming Gavi replenishment). Using vaccine bonds or an IFFIm mechanism for the COVID-19 effort could be one way to take pressure off these other mobilization efforts. The current crisis is an opportunity for high-level dialogue on ways to reform the overall financing system and to ensure complementarity of funding efforts.

# 1 INTRODUCTION: THE URGENT NEED TO DEVELOP AND MANUFACTURE COVID-19 VACCINES

## Key messages

The virus that causes COVID-19, the SARS-CoV-2 virus, has quickly spread worldwide. On January 30, 2020, the WHO declared COVID-19 to be a Public Health Emergency of International Concern (PHEIC) and advised all governments to prepare for transmission in their countries. On March 11, 2020, the WHO declared that it had become a pandemic. There is uncertainty about what will happen next, e.g., the pandemic could involve multiple waves of COVID-19 over 1-3 years and/or SARS-CoV-2 could become a globally endemic virus. We need to prepare for a worst-case scenario, in which the rapid development and scale-up of COVID-19 vaccines is critical to reducing the morbidity, mortality, and economic damage associated with a pandemic. Were SARS-CoV-2 to become endemic, any vaccines developed would likely find sustained global demand for their production. While the costs of development may be high (CEPI estimates the costs of clinical development and “scale-out” alone as up to US\$2 billion), the costs of inaction are much larger (the economic costs of COVID-19 in China alone are estimated to be US\$62 billion in the first quarter of 2020).

## 1.1 Current status of COVID-19

As of March 31 2020, at 1:28pm (ET), the Johns Hopkins University Center for Systems Science and Engineering [reported](#) that there have been 826,222 confirmed cases of COVID-19 infection and 40,708 deaths. In comparison, there were [774 reported deaths](#) from the 2003 SARS outbreak. The five countries hardest hit by COVID-19 have been the United States (174,467 cases), Italy (105,792 cases), Spain (94,417 cases), China (82,278 cases), and Germany (68,180 cases). China’s National Health Commission [reported](#) on February 14, 2020 that 1,716 health workers had been infected.

An initial [assessment](#) of the outbreak by Li and colleagues estimated that in the early phase of the COVID-19 outbreak in China, the epidemic doubled in size every 7.4 days and the basic reproductive number ( $R_0$ ) was 2.2. It has been challenging to accurately track the spread, because of factors such as the lack of rapid diagnostic tests and the mildness of the symptoms in some infected people.

The case fatality rate (CFR) has been the subject of much debate. The CFR for cases outside China was initially [estimated](#) to be 2.2% (95% confidence interval, 0.6%-5.8%). The [first clinical study](#) of COVID-19 in patients in Wuhan reported a much higher CFR, of about 15%, though this estimate may be [prone to detection bias](#). A more recent [study](#) of the symptomatic case fatality risk (the probability of dying from the infection after developing symptoms) in Wuhan found that the overall risk was 1.4% in patients aged 15 years or older.

Hospitalized patients in Wuhan had a high rate of transfer to the intensive care unit: a [study](#) by Wang and colleagues of 138 hospitalized patients found that 36 patients (26.1%) were transferred to the intensive care unit because of complications.

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There is no specific treatment, though a [large number of treatment trials](#) are now underway; on February 15, 2020 the WHO [estimated](#) that there were 82 trials of various MCMs (including of antiretrovirals and traditional Chinese medicines) being conducted in China.

## 1.2 Potential future scenarios

SARS-CoV-2 virus has rapidly spread worldwide and COVID-19 is now a pandemic, but future scenarios remain highly uncertain and will be affected by the suppression or mitigation strategies that countries use. For example, [modeling](#) by Ira Longini, co-director of the Center for Statistics and Quantitative Infectious Diseases at the University of Florida, an adviser to the WHO, suggests that up to two-thirds of the world could become infected. But other modelers argue this is a worst-case scenario, which even if true would be mitigated by the many people who would be minimally or mildly symptomatic.

Models and estimates are being refined as new information becomes available. For example, on March 16 2020 the Imperial College COVID-19 Response Team in London, which modeled the outbreaks in the UK and the US, [concluded](#) that “in an unmitigated epidemic, we would predict approximately 510,000 deaths in GB [Great Britain] and 2.2 million in the US, not accounting for the potential negative effects of health systems being overwhelmed on mortality.” Both the UK and US are now instituting suppression methods, such as social distancing.

A [study](#) by Wu and colleagues using flight data suggested that Beijing, Shanghai, Guangzhou, and Shenzhen were all at risk of substantial numbers of cases, and that “independent self-sustaining outbreaks in major cities globally could become inevitable because of substantial exportation of pre-symptomatic cases.” Bogoch and colleagues [projected](#) a high risk of spread from the Chinese mainland to Taipei, Bangkok, Tokyo, Seoul, Singapore, London, Sydney, Los Angeles, New York, Paris, San Francisco, Moscow, and Cairo. Efforts to contain the virus have clearly slowed its transmission, but at extraordinary cost, and it is unclear how long the quarantines and other measures employed can be maintained. While containment efforts continue for the time being, many experts now doubt that eradication can be achieved.

In addition to the possibility of multiple waves of COVID-19, there is also a [possibility](#) that COVID-19 becomes a globally endemic virus. Given the current pandemic situation, vaccine development has become an urgent priority.

## 1.3 Economic consequences of inaction

In addition to their major health consequences, previous epidemics and pandemics have also been associated with [large economic losses](#):

- The global economic loss from SARS in 2003 was US\$52.2 billion (more than US\$6 million per case)
- The 2014-2016 Ebola outbreak led to a direct loss of US\$2.8 billion across Guinea, Liberia, and Sierra Leone and an estimated global social and economic burden in excess of US\$53 billion (more than US\$1.8 million per case)
- The 2015 MERS epidemic in South Korea was estimated at the time to have resulted in economic losses approaching US\$10 billion (more than US\$50 million a case)

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- The 2015-2016 Zika outbreak led to an estimated loss of US\$3.5 billion in the Latin American and Caribbean region.

An early estimate of the economic losses from COVID-19 was that China was expected to lose up to [US\\$62 billion](#) in the first quarter of 2020. The global loss was estimated to be US\$280 billion within the same period. Oxford Economics [predicted](#) that China's economic growth in the first quarter of 2020 would be 4% lower than in the first quarter of 2019. It also expected the global economy to grow by 0.2 percentage points less as a result of COVID-19. More recent estimates paint an even starker picture. For example, economists at J.P. Morgan [forecast](#) "the Chinese economy to drop more than 40% this quarter and the U.S. economy to shrink 14% in the next," while Bloomberg Economics [estimates](#) that there could be a total of US\$2.7 trillion in lost output globally—equivalent to the entire GDP of the U.K. The anticipated economic losses are another reason why vaccine development is so urgent.

The Overseas Development Institute (ODI) [developed](#) a "vulnerability index" to estimate which countries are likely to be the most economically vulnerable to COVID-19. Based on countries' likely exposure to COVID-19 and their poor preparedness to address the economic impacts, the index predicts that the most vulnerable countries in economic terms are Sri Lanka, the Philippines, and Vietnam, followed by Kazakhstan, Kenya, Cambodia, and Nepal.

## 2 WHY FUNDING IS NEEDED FOR THE DEVELOPMENT OF COVID-19 VACCINES

### Key messages

CEPI has proposed three core goals for its vaccine development efforts—**speed**, **scale**, and **access**—goals that will entail large investments in a short time horizon and a high tolerance for risk. CEPI estimates that the costs of developing one or more vaccines, inclusive of clinical and process development with scale-up and potential transfer of manufacturing, are likely to be in the range of US\$2 billion. These cost estimates presume development to the point at which the vaccines can be licensed or used under emergency use provisions and *do not include* costs for subsequent manufacturing, delivery or administration.

Funding is needed for *all stages* of COVID-19 vaccine development. The first US\$100 million that CEPI is spending has come from unprogrammed funds already allocated to other projects (CEPI does not have an emergency response lockbox), so this funding also needs to be recouped.

While the urgent need is to develop COVID-19 vaccines, this crisis could potentially also be an opportunity to begin developing a sustained mechanism to mobilize new financing for development and product manufacturing for a broad range of EIDs and neglected diseases.

### 2.1 The valley of death in funding late stage development for EIDs and neglected diseases

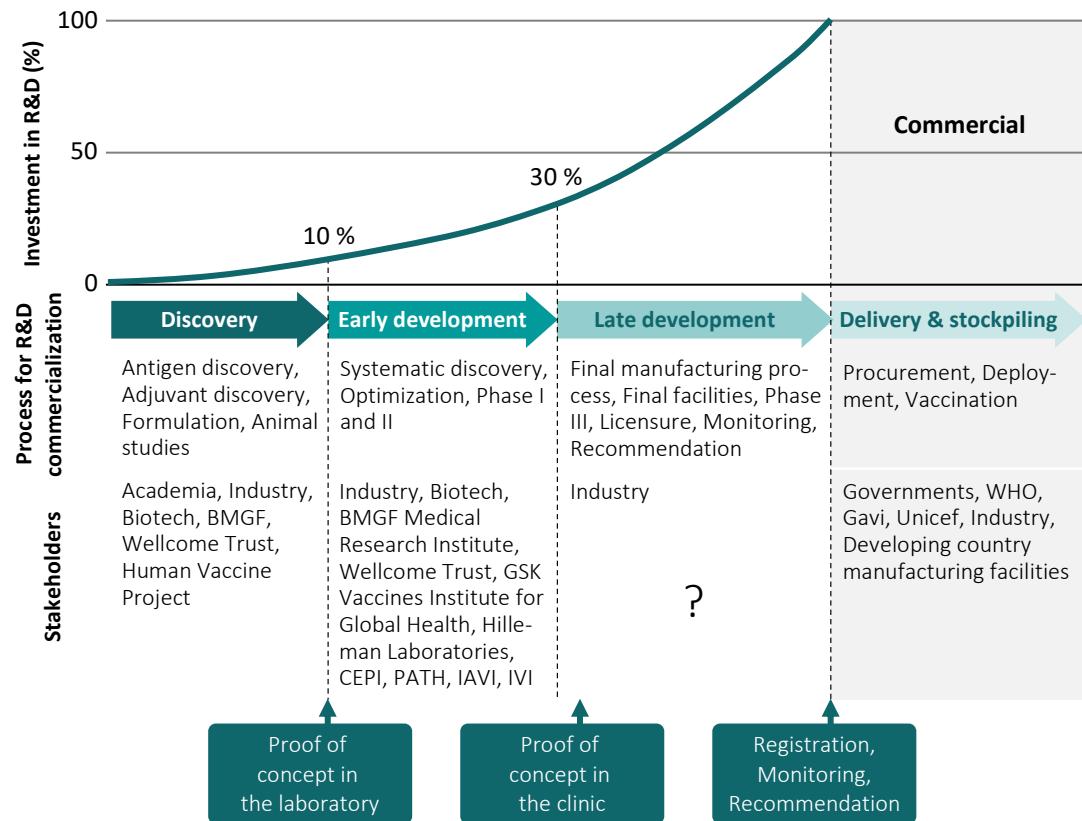
Research led by the Center for Policy Impact in Global Health at Duke University has illustrated a valley of death in the development of technologies to control both EIDs and neglected diseases. There is a large drop-off in the pipeline of candidates from phase II to III, which partly reflects the very high costs of phase III trials. For example, as of August 31, 2017, just 38 out of the 538 candidates (7%) in the pipeline for neglected diseases were in phase III.

At baseline, there is currently too little funding for late-stage trials, there are too few funders, and the financing is highly fragmented, creating inefficiencies. The result is that for many fatal or disabling conditions, the prospects for developing urgently needed control tools are very poor.

For vaccine development specifically, Rappuoli and colleagues have recently shown the high costs of late stage trials (Figure 2). While there have been improvements in early stage development, thanks to investments by the Bill & Melinda Gates Foundation, CEPI, PATH, and others, “these improvements in the early development process have revealed a new, and possibly more perilous, Valley of Death in the late vaccine development phase.” Late development is responsible for about 70% of total development costs. There is a major gap in the financing architecture for such late development (Figure 2 shows this gap, which is denoted by “?”). The large costs and time commitments are explained by the need to (a) produce vaccine candidates according to good manufacturing practice (GMP) standards in purpose-built production facilities, (b) conduct large-scale phase III trials, (c) submit data to regulators, and (d) conduct post-marketing surveillance. Although not shown in the figure, phase IV costs can also be substantial.

As described below, there are a number of promising COVID-19 vaccines in early development. However, unless dedicated funding is mobilized to fund this development, and then to fund late stage trials and manufacturing, these candidates will never be developed and deployed. As mentioned, CEPI has no emergency funds set aside, and so all stages of COVID-19 vaccine development need emergency funding.

While the acute, urgent focus is on funding for COVID-19 vaccine development, the current crisis reveals once again that we need to mobilize new financing, especially for phases III and manufacturing, for a broad range of health technologies for both EIDs and neglected diseases.



**Figure 2. Stages of vaccine development and delivery**

The figure shows three stages of vaccine development: discovery (10% of the R&D budget), early development (20% of the budget), and late development (70% of the budget). Under the graph are the funders and stakeholders involved at each step. A major gap can be seen in the financing architecture for late development (denoted by "?"). Figure adapted from a figure in: Rappuoli R, et al. Vaccines and global health: In search of a sustainable model for vaccine development and delivery. *Sci Transl Med.* 2019 Jun 19;11(497).

## 2.2 Status of current COVID-19 vaccines

CEPI is currently funding six candidates through Phase 1--one is now in Phase 1 development and the rest are still in pre-clinical development (Table 1). The platforms supporting these candidates are also being used to develop vaccines for other indications, several of which have reached clinical trials. CEPI aims to expand the portfolio to a total of up to 8 candidates. The portfolio needs such expansion, given (i) standard attrition rates

during development, and (ii) the fact that the current CEPI-funded development efforts involve partners [that](#) do not have the production facilities to make a commercial product in bulk at a scale commensurate with the needs in a pandemic. While all are using innovative techniques to fast track vaccine candidate development, none have licensed a vaccine. Thus, there are substantial barriers ahead with respect to manufacturing and licensure (see below).

There are [reports](#) of other COVID-19 vaccines being developed, including through a [collaboration](#) between Johnson & Johnson and BARDA, a [collaboration](#) between Sanofi and BARDA, and by Chinese government research organizations through [funding](#) by Jack Ma, Alibaba's founder. Several university efforts are also underway, [including](#) at the Baylor College of Medicine.

The first clinical trial of a COVID-19 vaccine candidate (mRNA-1273, see Table 1) [began](#) on March 16, 2020 at Kaiser Permanente Washington Health Research Institute in Seattle, Washington, USA. CEPI funded the manufacturing of this candidate for the phase 1 trial, and the NIAID is funding the trial itself. Two days later, a phase 1 trial [began](#) in China.

Other COVID-19 vaccine candidates could potentially be ready for clinical trials soon, and investments in process development and scale up of manufacturing could begin immediately, albeit at risk—hence the urgency to mobilize financing immediately.

**Table 1. The six COVID-19 candidate vaccines funded by CEPI as of March 17, 2020**

COVID-19 vaccine candidate	Developer	Funding from CEPI for COVID-19 vaccine development
INO-4800	Inovio pharmaceuticals	US\$8.9 million
Protein sub-unit (molecular-clamp vaccine platform)	University of Queensland	Up to US\$4.5 million
mRNA based vaccine	CureVac	US\$8.4 million
mRNA based vaccine (mRNA-1273)	Moderna Inc. in partnership with NIAID	US\$0.9 million for manufacturing (clinical trial costs covered by NIAID)
Multiple recombinant nanoparticle vaccine candidates plus an adjuvant (Matrix-M adjuvant)	Novavax	US\$4 million
ChAdOx1 vaccine platform (replication-deficient simian adenoviral vaccine vector), which has been used to produce vaccine candidates against multiple pathogens	University of Oxford	US\$0.4 million

## 2.3 Costs to develop and deploy a COVID-19 vaccine

### Key message

Up to US\$2 billion is needed to accelerate the development of, scale up, and prepare to roll out vaccines against COVID-19.

On February 14, 2020, CEPI produced a background paper called “Investment Case: Rapid Vaccine Development for COVID-19,” which it shared with us for the development of this paper. Since then, CEPI has made these estimates [public](#). CEPI estimates that:

- Up to US\$2 billion is needed to “accelerate the development of, scale up, and prepare to roll out vaccines against 2019-nCoV [now called COVID-19]
- The best-case scenario would see vaccines that could potentially be deployed, whether as a licensed product or under appropriate ‘emergency use provisions’ within 12-18 months.”

The US\$2 billion estimate is based on the following:

- “Funding for an initial 8 vaccine candidates from preclinical through phase I, with clinical development cost up to \$10m for each.
- Support for scale up, process development and manufacturing, at risk,<sup>a</sup> while candidates are in phase I. Such investment will allow for the rapid initiation of phase 2/3 trials. The assumption is that initial investments would be required in all 8 candidates for an average of close to \$70m for each of those candidates.
- CEPI progresses 6 vaccine candidates through phase II/III, with clinical development costs up to \$150m each including Clinical Trial Material cost.
- If CEPI were to progress 3 vaccine candidates to full licensure there would be additional costs of up to \$100m per candidate.”

CEPI cautions that these are indicative budget estimates based on professional judgment and do not reflect specific budgets from the current set of performers.

These cost estimates presume development to the point at which the vaccines can be licensed or used under emergency use provisions and *do not include* costs for subsequent manufacturing, delivery or administration.

<sup>a</sup> “At risk” in this context means beginning the investment in process development and scale-up without even knowing whether the vaccine candidate works. The process development and scale-up, in theory, are agnostic of the vaccine candidate, so that if a particular candidate failed and a new construct has to be developed, the investment has not gone to waste. It only goes to waste if the particular development program is cancelled altogether (which it might be if the candidate failed while others succeed).

### ③ MOBILIZING AN ADDITIONAL US\$2 BILLION FOR COVID-19 VACCINE DEVELOPMENT AND DEPLOYMENT

#### Key messages

Closing the US\$2 billion funding gap will require contributions from the public, philanthropic, and private sectors, including from official development assistance (ODA) and domestic health investments. All countries are at risk, and must be prepared, which means there is a strong case for all governments to invest in COVID-19 vaccine development and deployment as part of their health systems preparedness investments. There is also an opportunity to use innovative finance mechanisms, such as vaccine bonds, advanced market commitments, as well as instruments within the World Bank's health portfolio, such as contingent emergency response components. It may be valuable to match different types of financing instruments with different steps in the vaccine development and deployment process.

#### 3.1 Public, philanthropic, and private sources

Given the scale of the threat, and the urgent need for additional financing, an “all of the above” approach is needed to close the funding gap, including new and additional ODA commitments (ODA should not be diverted or “cannibalized” from other key health investments). Many donors have already shown their commitments to the COVID-19 vaccine response, [including](#) to the WHO’s COVID-19 appeal. Norway [pledged](#) NOK36 million and the United Kingdom [pledged](#) GBP£20 million to CEPI for COVID-19 vaccine development. On March 17 2020, the World Bank Group [approved](#) a “\$14 billion package of fast-track financing to assist companies and countries in their efforts to prevent, detect and respond to the rapid spread of COVID-19.”

All governments need to prepare for transmission of the SARS-CoV-2 virus in their countries, and investment in the development and deployment of a vaccine against COVID-19 is a critical component of preparedness. Thus, alongside *new* ODA, there is a strong rationale for OECD governments to tap into the budgets of their health ministries (as part of their health systems investments aimed at pandemic preparedness) and their ministries of science and technology to fund advanced development and deployment of a COVID-19 vaccine. For those emerging economies with the means to do so, there is a similar rationale for these governments to also support the COVID-19 vaccine funding window.

Following the lead of the Bill & Melinda Gates Foundation, which recently [committed](#) US\$100 million in response to the epidemic, and the Wellcome Trust, which [pledged](#) GBP£10 million, philanthropic funding can help close the gap.

There is an important role for the private sector, not just in providing in-kind expertise but also as co-investors—along with the public and philanthropic sectors—in vaccine development and deployment. As the cascading consequences of the COVID-19 epidemic in China demonstrate, private sector companies are increasingly dependent on global supply chains (or on parts of the supply chain located in low-income countries and MICs) and they have a strong economic incentive to invest in the development of vaccines, in addition to any moral compulsion they may feel.

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## 3.2 Innovative financing approaches

### Vaccine bonds

The International Finance Facility for Immunisation (IFFIm) was launched in 2006 to rapidly accelerate the availability and predictability of funds for immunization. IFFIm uses the financial markets—through the issuance of bonds—to turn long-term contributions by donor countries into current, or “frontloaded,” cash. IFFIm supports Gavi’s vaccine programs and to date has received legally binding pledges from ten donors totaling about US\$6.6 billion spanning 23 years to 2030. The World Bank is IFFIm’s treasury manager. In June 2019, Norway pledged NOK600 million (US\$66 million) to IFFIm to support CEPI’s vaccine development efforts. IFFIm bonds are therefore an existing finance model that could be used to help finance the development and deployment of a COVID-19 vaccine. Such IFFIm bonds could be blended with direct contributions from donors. Gavi’s Board recently [expressed support](#) for using IFFIm to improve COVID-19 vaccine development and access.

### The Pandemic Emergency Financing Facility (PEF)

An alternative bond-based mechanism is the PEF, [launched](#) in July 2017, which includes both a cash window and an insurance window. The PEF is currently undergoing review, including a review of the activation criteria for the insurance window (which have been [criticized](#) for being too narrow). “PEF 2.0” is due to be launched by May 2020. While PEF’s cash window could potentially also be used for funding the development and/or manufacturing and delivery of a pandemic vaccine, this is not an approach that has been fully tried and tested.

### Advanced market commitments (AMCs)

To de-risk the efforts of manufacturers (described further in Section 6.1), an AMC could be used. Gavi’s AMC for pneumococcal vaccines, for example, guarantees the price of vaccines once they have been developed.<sup>b</sup> Funding commitments by donors provide vaccine manufacturers with the incentive they need to expand manufacturing capacity (there is some debate on whether AMCs could potentially also stimulate R&D). In exchange, companies sign a legally binding commitment to provide the vaccines at a price affordable to developing countries in the long term. Another example is the advanced purchase commitment (APC) between Gavi and Merck. Based on a pre-payment made by Gavi, Merck committed to create a stockpile of its Ebola vaccine, which is being used in the DRC today. Gavi’s board has [supported](#) the use of AMCs in development and deployment of COVID-19 vaccines.

### World Bank instruments

A number of instruments within the World Bank’s health portfolio, such as contingent emergency response components, could also be leveraged.

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## 3.3 Matching different financing instruments with different steps in vaccine development

Each of the different financing instruments discussed above may be better suited to funding particular stages of COVID-19 vaccine development. An illustrative schematic of this kind of matching is shown in Figure 1 on page 2. How to mix and match funding instruments requires further exploration.

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<sup>b</sup> Though CEPI itself would not issue an AMC—it would hand off products ready for stockpiling to other partners in the ecosystem, such as Gavi.

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## 4 CEPI AS A VENUE FOR FUNDING LATE STAGE DEVELOPMENT OF COVID-19 VACCINES

### Key messages

If provided with sufficient resources, CEPI is an existing platform with scientific expertise and networks that could be leveraged to support and oversee the first three steps in the COVID-19 vaccine development process: pre-clinical development, clinical development, and “scale out.” It would not be the right vehicle for funding manufacturing of vaccine for general use or its delivery, which are outside CEPI’s remit. By using an existing platform as the “add-on” venue for funding advanced development of COVID-19 vaccines, transaction costs would be lower than launching a new mechanism. Additional expertise on funding phase III trials and in tech transfer through CEPI could be quickly incorporated without large investments. Once this expertise and funding window for late stage development is in place, the window would be “ready to go” for future outbreaks. CEPI’s existing equitable access policy appears to be flexible enough to apply to the expansion of CEPI-funded activities to phase III trials and beyond and its existing governance arrangements have flexibility to adapt to the expanded scope of work contemplated by this new financing window. CEPI is already supported by a World Bank financial intermediary fund (FIF), and so using this existing FIF to finance advanced development of COVID-19 vaccines would allow for speed, low transaction costs, flexibility, and global access.

### 4.1. The advantages of CEPI as a venue for funding late stage development of COVID-19 vaccines

Although CEPI is only three years old (Box 1), it has established expertise in financing the development of a broad suite of epidemic and pandemic vaccines. It has already shown that it can very quickly fund COVID-19 vaccine developers and expand the portfolio of candidates under development. It has strong relationships with key stakeholders in ensuring the late stage development and deployment of a vaccine, including regulators, WHO, Gavi, industry, academics, and foundations. CEPI has some experience already with funding phase III trials. Assuming the collaboration of the private sector partner, CEPI can target its investments to complement those of governmental institutions such as BARDA that may also be making substantial investments in COVID-19 vaccine development.

Furthermore, CEPI is supporting rapid response vaccine platform technologies partnerships (e.g. with Imperial College London, CureVac, and University of Queensland) that could potentially shorten the time it takes to develop vaccines from years to weeks.

Using CEPI—as an existing institution—for the first three steps in COVID-19 vaccine development makes strategic sense in terms of speed and keeping transaction costs down. There is existing expertise and institutional capacity within CEPI that could be further strengthened without large investments or substantial amounts of time. Once such a window is established, it could be leveraged for other future outbreaks.

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**Box 1: About CEPI**

- CEPI's mission is to stimulate and accelerate the development of vaccines against emerging infectious diseases and enable access to these vaccines for people during outbreaks.
- CEPI was launched in January 2017 at the World Economic Forum in Davos, Switzerland.
- Its current focus is on early development. However, it can fund phase III trials in certain circumstances where there is a clear need and when it can mobilize funding (e.g., it will fund [late stage trials](#) of two Chikungunya candidate vaccines).
- CEPI's first call for proposals was for the development of vaccines against MERS-CoV, Nipah virus, and Lassa virus, all of which are on the WHO's [R&D Blueprint list for Action to Prevent Epidemics](#). These three pathogens were [prioritized](#) "based on a set of criteria including the risk of an outbreak occurring, transmissibility of the pathogen, burden of disease, and feasibility of vaccine development."
- Its second call was for "the development of platforms that can be used for rapid vaccine development against unknown pathogens." This call has now been re-opened to invite additional partners to apply. Of the first four COVID-19 vaccine candidates under development funded by CEPI (the top four rows in Table 1), one was funded from the first call (Inovio, which had a MERS Co-V vaccine in phase I trials), two were funded from the second call (CureVac and the University of Queensland), and one was from a new call (Moderna Inc.).
- Its [third](#) call was for the development of vaccines against Chikungunya and Rift Valley fever.
- CEPI has received unrestricted multi-year funding from Norway, Germany, Japan, the United Kingdom, Canada, Australia, Ethiopia, the Bill & Melinda Gates Foundation, Wellcome, and the European Commission. It has received restricted multi-year funding from India, a single-year investment from the government of Belgium, and co-funding from the European and Developing Countries Clinical Trials Partnership. It has reached ~US\$850 million of its US\$1 billion funding target for the period 2017-2021.

## 4.2. The advantages of using a World Bank financial intermediary fund (FIF)

CEPI is supported by a World Bank FIF. As the beneficiary of a FIF, there would be many advantages to using CEPI as a vehicle for funding both early and late stage development of COVID-19 vaccines. Unlike IDA/IBRD, FIFs allow for contributions from non-government stakeholders, such as private philanthropy or the private sector. FIF recipients are not limited to Bank-eligible countries. The World Bank's role in FIFs is flexible: at a minimum, a FIF is a financial pass-through where use of funds is solely determined by the governing body. The World Bank can also provide program management functions and implementation support. The governance arrangements and design of FIFs are also highly flexible. FIFs can disburse funds rapidly.

Core IBRD/IDA programs can accept contributions only from governments, but FIFs can accept funding from the private sector. FIFs have several other benefits. For example:

- They can channel funding to countries that are not members of the Bank or do not choose to invest in global public goods. For example, from 2006-2013 [the Avian and Human Influenza Facility](#) raised US\$126 million for avian influenza surveillance and control and allocated some of this funding to "weak link" countries that were not prioritizing influenza control interventions.

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- FIFs are usually able to disburse funds more rapidly than core IBRD/IDA funding mechanisms because they sidestep traditional bank administrative and operational processes. For example, unlike in core lending, the bank's board of executive directors usually are not required to approve FIF proposals. This ability to harness political momentum has been crucial in launching many global health programs targeting infectious diseases.
  - The narrowly defined goals and measurability of outcomes of projects funded by FIFs make them attractive to funders.

### **4.3 A funding vehicle for manufacturing and procurement**

CEPI does not have expertise in funding or managing the fourth and fifth steps in vaccine development (Figure 1), which are outside of its remit. A distinct consortium of public and philanthropic funders is likely to be needed.

### **4.4 Breaking the cycles of panic and neglect: towards a sustained funding approach**

Establishing the kind of funding approach for development and deployment of COVID-19 vaccines shown in Figure 1 could be the start of a new, coordinated approach to funding MCMs for epidemic and pandemics. Once established, this approach could be used for future outbreaks—not just for vaccines but also diagnostics and therapeutics (antivirals and monoclonals).

The “valley of death” in funding phase III trials and manufacturing of health tools for controlling EIDs also applies to neglected diseases more broadly. This new approach for COVID-19 vaccine financing could be an important step in developing a sustained pooled funding platform for late stage development and deployment of new technologies to control other EIDs and diseases of poverty. In other words, this new approach would set a precedent and it would lay the groundwork to fund late stage development/deployment of technologies to control an array of diseases of poverty.

## 5 GOVERNANCE OF NEW COVID-19 VACCINE FUNDING CHANNELED THROUGH CEPI

### Key messages

CEPI's existing governance arrangements—a Board with 12 voting members that is guided by a Scientific Advisory Committee (SAC) and a Joint Coordination Group—are flexible enough to adapt to the expanded scope of work contemplated by this new financing for late stage COVID-19 vaccine development.

Since its launch, CEPI has announced three calls for proposals (Box 1), and CEPI's Board approves all funded projects. The [Board](#) has 12 voting members (“four investors and eight independent members representing competencies including industry, global health, science, resource mobilisation, finance”) and five observers (including WHO and the World Bank). Currently, one third of Board members are based in low- or middle-income countries. There are four Board committees: Executive and Investment, Compensation and Nomination, Audit and Risk, and Equitable Access. The Board receives support and advice from the SAC and a Joint Coordination Group.

Investor Board members are invited to join CEPI's [Investors Council](#), which “nominates Investor representatives to the Board and has some rights including approval of any single investment over \$100m.” The [SAC](#) has 24 voting members and five non-voting members. It provides scientific support and advice, e.g. it provides scientific guidance on CEPI's calls for proposals and it recommends which pathogens should be prioritized for vaccine development. The SAC does not have decision-making authority over CEPI's operations. CEPI's [Joint Coordination Group](#) is a “roundtable of independent institutions with an interest in seeing CEPI's vaccines successfully developed and deployed in an outbreak.”

It would be relatively straightforward to modify these arrangements, e.g. by expanding the SAC's expertise to include experts on late stage trials and manufacturing and potentially adding new investors to the Investors Council.<sup>c</sup> CEPI considers the inclusion of strong representation of LICs and MICs in its development programs essential and such representation should be reflected in any expanded governance and oversight arrangements related to the management of the COVID-19 portfolio.

<sup>c</sup> CEPI's Investors Council has made it clear that only investors making *unrestricted* donations gain full governance privileges (investors who restrict their donations gain such privileges). CEPI could adapt, however, to provide appropriate transparency and oversight to investors in the COVID-19 vaccine development effort, perhaps by establishing some kind of “COVID-19 Investors Board,” but this would require discussions with the CEPI Board.

## 6 ADDRESSING CHALLENGES IN MANUFACTURING, INTELLECTUAL PROPERTY, ACCESS, AND REGULATORY APPROVAL

### Key messages

For the current set of COVID-19 vaccines supported by CEPI funding, none of the partners has experience in bulk manufacturing and they have not previously licensed a vaccine. For manufacturing at scale, it is likely that a consortium of manufacturers—including MNCs, CMOs, and DCVMs—will be needed to produce the large numbers of doses that may be required (e.g. a billion doses in 12-18 months from now). A new public-private partnership model for bulk manufacturing of COVID-19 vaccines by such a consortium of manufacturers is likely to be needed. CEPI's existing equitable access policy appears to be flexible enough to apply to the expansion of CEPI-funded activities to phase III trials and beyond. Regulatory agencies and bodies recognize the urgency of providing a simplified and expedited, joint regulatory review of COVID-19 MCMs. It will be critical to avoid a scenario in which high-income country governments enter into bilateral purchase contracts with manufacturers, thus monopolizing the vaccine. In the current pandemic scenario, which may involve waves of COVID-19 over many years, one global access model would be for the vaccine to be procured with public funding and allocated as close to pro rata as possible to countries.

### 6.1. Manufacturing the COVID-19 vaccine

In a worst-case scenario, a very large number of COVID-19 vaccine doses will need to be manufactured in a short time period. Establishing large-scale manufacturing capacity for a coronavirus vaccine is a key challenge to be overcome. To produce the needed volumes of vaccine, a large MNC (or several companies) will likely have to be engaged in some way. Yet the large MNCs are wary of being asked to manufacture epidemic and pandemic vaccines because of the high opportunity costs (they have to take a commercially successful product off one of their manufacturing lines); they also fear that tech transfer could lead to them losing commercially valuable IP. Such companies *feel* “burned by the string of vaccine pleas,” and are unsure that they can “afford these costly disruptions to their profit-seeking operations.”

However, as discussed below (section 6.2), COVID-19 could end up being an endemic global pathogen, and in this scenario, it could be highly profitable for MNCs to manufacture the vaccine and sell it using a tiered pricing model. Thus, in comparison to other outbreaks, such as Ebola, we may see MNCs being much more willing to manufacture a vaccine for COVID-19.

There is also vaccine manufacturing capacity in many MICs, such as China and India, and these companies could be highly incentivized to step up their role. CEPI has recently conducted a global survey of such capacity. Rapid tech transfer to these companies in MICs for manufacturing is likely to be part of the solution.

For COVID-19 vaccines under development, CEPI has forged partnerships with biotech companies, a government scientific agency, and a university. CEPI has entered a partnership with one MNC already, GSK, to make its adjuvant technology available. However, to ensure the large-scale production of the vaccine, a new public private partnership model for bulk manufacturing of the COVID-19 vaccine by a consortium of manufacturers (MNCs, CMOs, and MICs) will probably be needed.

## 6.2 Intellectual property

CEPI outlines its commitment to access in its [equitable access policy](#) (Box 2), which can be applied to ensure global access to a COVID-19 vaccine. CEPI [revised](#) its original equitable access policy last year. The impetus for this change was its desire to provide greater flexibility as to the means of ensuring equitable access to vaccines and to attract more potential industry partners. Although the overarching principles of the original equitable access policy remain intact, the new policy takes a more “principles-based” than “rules-based” approach. This approach allows CEPI to have more flexibility in negotiations with partners, although the shift has attracted [scrutiny](#) from some stakeholders.

In both the new and the old policy, CEPI does not take ownership over IP. However, it can use its “[step-in rights](#)” to move a candidate forward if the awardee is “unable or unwilling to further vaccine development and equitable access.” The triggers that would cause such an action are unique to the negotiated contract for a particular product.

Under the new policy, “stage-gate reviews” are to be used to review compliance with the equitable access mandate (Box 2) at each major stage of development and testing. If a company cannot keep its commitment to making a product available or affordable, CEPI could, according to its negotiated terms, identify a new awardee to which to transfer the IP.

Moving forward, CEPI [intends](#) to adapt the terms of negotiation for each call for proposal round. CEPI’s equitable access policy can probably accommodate the unique elements of funding phase III trials and manufacturing. Based on CEPI’s [existing model](#), a call for phase 3 COVID-19 testing could embed its own unique requirements, different from those for other products. The flexibility of CEPI’s access policy also ensures both CEPI and the awardee are in alignment regarding both the price and the terms that would be used to activate CEPI’s “step-in rights.”

### Box 2: CEPI’s equitable access policy

Equitable access is at the heart of CEPI’s mandate, and was defined in its 2019 revised equitable access [policy](#): “Equitable access to epidemic vaccines in the context of an outbreak means that appropriate vaccines are first available to populations when and where they are needed to end an outbreak or curtail an epidemic, regardless of ability to pay.” CEPI’s approach is grounded in several guiding principles that allow for flexibility in partner agreements and negotiations, all of which must meet agreed upon thresholds for ensuring equitable access.

CEPI aims to facilitate equitable access to epidemic and pandemic vaccines by:

- (1) Funding the development of vaccines and maintaining investigational stockpiles, to be used free of charge when an outbreak occurs
- (2) Coordinating with others in the global health community to enable licensure of vaccines funded by CEPI, including by securing resources for pivotal clinical trials
- (3) Collaborating with others in the global health community to ensure the procurement, allocation, deployment and administration of licensed vaccines to protect global health, at a price that does not limit equitable access and is sustainable to the manufacturer.”

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### **6.3 Ensuring global access**

Affordability and accessibility must be the bedrock of any proposal for a new funding push for COVID-19 vaccine development. The poor are hit “first and worst” by outbreaks, and any access model that ends up giving only high-income countries access to the vaccine would clearly be unacceptable. It will be critical to avoid a scenario in which high-income country governments enter into bilateral purchase contracts with manufacturers, thus monopolizing the vaccine.

In the current pandemic scenario, which may involve waves of COVID-19 over many years, one global access model would be for the vaccine to be procured with public funding and allocated as close to pro rata as possible to countries. In this scenario, countries would probably need some additional way to prioritize who receives the vaccine. The consortium of manufacturers discussed earlier (MNCs, CMOs, and MICs) would ideally provide a “cost plus” contract (with a small margin) for sales to a global purchasing agent for a time-limited period; the vaccine would be free at the point of care. If COVID-19 then transitions to become a globally endemic pathogen, a tiered pricing model could be adopted.

### **6.4 Expediting regulatory approval**

During the 2014-2016 Ebola epidemic in west Africa, there was widespread agreement that a [new mechanism](#) was needed to rapidly agree on trial designs and to collaborate across borders on fast-track scientific assessment, regulatory approval, and roll-out. For example, the African Vaccine Regulatory Forum [proposed](#) that this mechanism would cover

- “Clear pathways and timelines for expedited ethical and regulatory review of clinical trial applications and approval of products;
- Agreement on timelines and joint safety and efficacy assessments of the new products to fast-track national registration;
- Endorsement of a panel of safety experts for expedited review of safety data of new products with relevant communication to National Regulatory Authorities (NRAs);
- Technical assistance from the World Health Organization (WHO) to facilitate these processes.”

Regulatory agencies and bodies, including the WHO, US Food and Drug Administration, European Medicines Agency, and the International Coalition of Medicines Regulatory Authorities, recognize the urgency of providing a simplified and expedited, joint regulatory review of COVID-19 MCMs. There is widespread recognition that a “business as usual” approach is not tenable.

## 7 CONDUCTING LATE STAGE TRIALS IN THE MIDST OF THE OUTBREAK

### Key messages

International experience of conducting phase III trials during epidemics, including Ebola (Box 3), has highlighted several key lessons and principles that should be adopted by the new funding window. These lessons relate to issues such as trial design (including the use of adaptive trials), the ethics of trial conduct, and being sensitive to the needs of communities. In light of the COVID-19 outbreak, on January 20 2020, the Nuffield Council on Bioethics [issued](#) a “Call for Action to research funders, governments, and others involved in health research systems for a more ethical and collaborative approach to conducting research during emergencies such as infectious disease outbreaks.”

#### **Box 3: Conducting trials during outbreaks: what can we learn from the 2014-2016 Ebola epidemic in West Africa?**

By the end of the 2014-2016 Ebola epidemic, more than ten therapeutic trials had been designed but none had been fully completed. As of 2019, there were 42 ongoing Ebola vaccine trials. For highly infectious and deadly diseases such as Ebola virus disease and COVID-19, conducting conventional clinical trials is very challenging. The Merck vaccine rVSV-ZEBOV is currently the only approved vaccine against Ebola virus; phase I trials started shortly after WHO declared the West Africa Ebola virus outbreak as a PHEIC. Regulatory approval came five years later. In addition to the common challenges of time and cost, there are ethical challenges in conducting vaccine trials in outbreaks. For example, it is difficult to justify processes such as randomization when only some patients receive a potentially lifesaving intervention. The Ebola trials pointed to the need for adopting new, more efficient clinical trial designs. One of these designs is an alternative platform trial using a “response adaptive randomization strategy” that allows for re-allocation of study participants based on treatment response, as was [proposed](#) during the Ebola epidemic.

### **7.1 Design of trials conducted during emergencies**

There are several challenges in conducting clinical trials during epidemics:

- **Time to enroll and complete a trial:** The duration of an epidemic is unpredictable, and control efforts are aimed at shortening the duration. Unless trials are started early, these factors make it difficult for trials to reach a conclusion before the epidemic burns out.
- **Enrolling a sufficient number of patients:** Clinical trials require minimum sample sizes in order to be sufficiently powered to make scientific conclusions. Enrolling enough patients is often impossible in short-run epidemics. A trial run by Gilead in Wuhan, China, of an antiretroviral to treat COVID-19 is [struggling](#) to recruit patients,
- Capacity for conducting clinical trials: When epidemics occur in low-resource settings, the capacity to conduct a clinical trial may not exist and researchers do not have the luxury of time to build capacity before conducting the trial.
- Resources: Large phase III trials are very costly, which is one rationale for launching a new funding window.

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- **Ethical challenges of using investigational new drugs:** There are often major arguments about compassionate use versus waiting for trial results. A WHO advisory panel [stated](#) that compassionate use is “justified as an exceptional emergency measure” but said that it should not “preclude or delay the initiation of more conclusive investigations of the intervention(s) in properly designed clinical studies.”

Policymakers face a number of important decisions, including (a) choosing the right candidates for inclusion in a trial (limited numbers of patients and resources mean that candidate selection is critical), and (b) choosing the right trial design (some trial designs work better for different situations). A number of solutions and advances have been developed to help meet these challenges, e.g.,

- **Adaptive clinical trials:** Adaptive trials, which use “results accumulating in the trial to modify the trial’s course in accordance with pre-specified rules,” are widely believed to be an important design advance for future outbreaks. Most evidence to date has been based on simulation studies, which show that adaptive trials have a higher potential to reach a decision during the outbreak than regular trials. Nevertheless, adaptive trial designs must take into account a [number of issues](#) (e.g. “whether the adaptation process has led to design, analysis, or conduct flaws that have introduced bias that increases the chance of a false conclusion that the treatment is effective”).
- **Stepped wedge trials:** in such trials, the intervention is introduced by random allocation at regular intervals to a cluster of participants until all clusters eventually receive the intervention. This design primarily addresses the ethical challenge of enrolling some affected populations in trials while excluding others.
- Non-randomized trials: these remain controversial and hard to interpret, but they could allow trials to be conducted when the capacity to conduct randomized trials is absent.
- Capacity building: An example is the [Clinical Research During Outbreaks \(CREDO\)](#) program, jointly funded/implemented by TDR, the International Severe Acute Respiratory and Emerging Infections Consortium, and the UK Public Health Rapid Support Team.

## 7.2 Ethical concerns in conducting trials in an outbreak situation

Too often, the ethical issues involved in conducting trials during epidemics or pandemics—including those related to community consultation and participation—have not been carefully considered *before* trials begin. These issues should not be an “afterthought” but should be front and center of this new vaccine funding window.

In January 2020, after a two-year study conducted by an international working group, the Nuffield Council on Bioethics published its [report](#), “*Research in global health emergencies: ethical issues*.” The report argued that research in emergencies should be guided by an “ethical compass” comprising three key values: equal respect (treating others as moral equals), helping reduce suffering (acting on duties founded on solidarity and humanity), and fairness (duties of non-discrimination and of “the equitable distribution of benefits and burdens”).

The report makes wide-ranging recommendations to research funders, WHO and other international agencies, governments, researchers, research ethics committees, and other stakeholders. These are summarized in a [Call for Action](#) (Box 4) that has been endorsed by many research organizations and

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international institutions, including the Wellcome Trust, the African Academy of Sciences, and the International Rescue Committee.

**Box 4: Nuffield Council of Bioethics' Call for Action on the ethical conduct of health research in emergencies**

"We are issuing a call for action to research funders, governments and others to:

- Ensure that research is not supported unless the basic health needs of research participants are being addressed through the response effort. Research funders will need to work in partnerships with humanitarian organisations and ministries of health to ensure this.
- Invest in putting community engagement mechanisms into emergency research to make them a reality. In the longer term, engagement must be a central part of local healthcare systems to ensure sustainability and preparedness.
- Promote fair and equitable collaborations between research organisations, particularly between external research institutions and their local partners in high- and low-income settings.
- Support emergency planning - including securing robust health and health research systems - given the vital importance of properly resourced preparedness between emergencies. "

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## 8 CONCLUSIONS

The global health community must prepare for a worst-case scenario, in which a vaccine will be a critical control tool. While there are several promising vaccine candidates, these could languish in early stage development unless new funding is mobilized to fund all stages of COVID-19 vaccine development and to manufacture the large number of doses that could be needed.

Funding early development through phase 3 trials and “scale-out” under CEPI, an existing platform, offers the advantages of speed, flexibility, and low transaction costs. Additional capacities required to support the later stages of development could be quickly added. CEPI’s existing governance arrangements and equitable access policies could be adapted for phase III/manufacturing without major obstacles. But manufacturing and delivery would require a separate financing mechanism outside of CEPI; a consortium of public and philanthropic funders is likely to be needed. Different financing instruments are likely to be better suited to financing different steps in the COVID-19 vaccine development process.

Ethical conduct of trials, participation of LICs and MICs in governance arrangements, and global access to the vaccine must all be cornerstones of this new funding approach. Innovations in trial designs (e.g. adaptive trials) and manufacturing (e.g. modular approaches) and joined-up approaches to expediting regulatory approval could help to streamline development and deployment of the vaccine.

A new funding approach for late stage trials and manufacturing of a COVID-19 vaccine could be the start of a new, coordinated approach to funding MCMs for epidemic and pandemics, one that helps to break [the cycles of panic and neglect](#). Once established, the approach could be used for future outbreaks—not just for vaccines but also diagnostics and therapeutics. It could also be an important step in developing a sustained and consolidated pooled funding platform for late stage development and deployment of new technologies to control a broad range of diseases, including EIDs and poverty-related and neglected diseases. Due to the lack of a well-resourced funding mechanism for late-stage trials, the prospects for developing urgently needed control tools for many fatal or disabling conditions are very poor.

Finally, additional funding is clearly needed for development and deployment of COVID-19 vaccines, but this effort should be *complementary* to other fund-raising processes (e.g. the Gavi replenishment and WHO’s mobilization of resources for pandemic response and preparedness). Using vaccine bonds or an IFFIm mechanism for the COVID-19 effort could be one way to take pressure off these other mobilization efforts. The current crisis is an opportunity for high-level dialogue on ways to reform the overall financing system and to ensure complementarity of funding efforts.