CEPI

Delivering Pandemic Vaccines in 100 Days

what will it take?

2022

Executive Summary

The development and authorisation of novel vaccines against SARS-CoV-2 in less than a year is a triumph of scientific and technological innovation. However, despite these accelerated development timelines, more than 70 million COVID-19 cases and 1.6 million resulting deaths were recorded worldwide before the first vaccine, BNT162b2 from Pfizer-BioNTech, received authorisation for emergency use, by which point the pandemic had become unstoppable. A more rapid response that contained the spread of the virus could have significantly limited the human and socio-economic cost of the pandemic.

In recognition of the potential impact that earlier, widespread availability of vaccines could have, CEPI has articulated an aspirational goal: ***vaccines should be ready for initial authorisation and manufacturing at scale within 100 days of recognition of a pandemic pathogen, when appropriate.*** Coupled with improved surveillance providing earlier detection and warning, and with swift and effective use of non-pharmaceutical interventions such as testing, contact tracing and social distancing to suppress disease transmission, delivering a vaccine within 100 days would give the world a better chance of containing and controlling future pathogenic threats and averting the type of catastrophic global public health and socio-economic impacts caused by COVID-19. These efforts should have a strong focus on increasing capabilities in LICs and LMICs and enabling equitable access to products once developed – no one is safe until everyone is safe.

CEPI has undertaken an in-depth exercise to identify innovations that could accelerate the development process and challenges that would need to be overcome to meet the 100-day aspiration. This exercise draws on joint research carried out between CEPI and McKinsey & Company, which included interviews with 46 representatives from vaccine-development firms, international organisations, regulatory agencies, academia, and the media, along with an extensive review and analysis of publicly available information.

This paper describes the findings of this exercise, focusing on the factors that enabled such rapid development of COVID-19 vaccines to develop a consensus around the most condensed timeline under which vaccines could be developed if these lessons were applied. It then describes a substantial shift from the current vaccine development paradigm necessary to deliver a vaccine for initial use within 100 days, and highlights areas of scientific and technological advancement that could underpin this shift. Recognising that innovations in research and development can only deliver global, real-world impact if they are made equitably accessible and are implemented in a supportive financing and governance ecosystem, the paper then discusses the requirements of an effective enabling pandemic preparedness and response ecosystem. Finally, the paper describes the investments and activities that CEPI and others are undertaking towards achieving the 100-day aspiration.

This paper focuses very deliberately on the technical and scientific innovations in vaccine development required to achieve speed in responding to an outbreak. This focus on speed should not distract from the importance of achieving scalability of manufacturing and ensuring equitable access to all in need of being protected during an outbreak, regardless of geographic location or ability to pay. Finally, we acknowledge that enabling the 100-day aspiration would come with a number of risks which would need to be extensively evaluated in advance of a pandemic, and the goal should be pursued only if the right safeguards, particularly regarding safety risks, are put in place.

Accelerated vaccine development during the COVID-19 pandemic

The development timelines from the day the COVID-19 sequence was made available until emergency use authorisation by a stringent regulatory authority or issuance of an Emergency Use Listing (EUL) by the World Health Organization (WHO) ranged from 326 to 706 days for the vaccines evaluated[1]. To understand the factors that enabled accelerated vaccine development during the COVID-19 pandemic, this exercise evaluated the development and authorisation timelines of COVID-19 vaccine candidates that, as of October 2021, were either approved by a stringent regulatory authority or issued with an EUL by the WHO. The exercise identified a catalogue of 37 innovations that contributed to accelerated development, early manufacturing and authorisation of COVID-19 vaccines. These innovations can be categorised into five broad areas and are underpinned by three core principles: prior knowledge available for deployment; multiple processes running wholly or partly in parallel; and significant collaboration between stakeholders globally.

Key areas of innovation contributing to accelerated development and authorisation of COVID-19 vaccines

1. Leveraging pre-existing insights about pathogens and platforms

- Building on experience from previous outbreaks of pathogens within the same virus family, including SARS-CoV-1 and MERS
- Benefitting from significant prior investment in novel rapid response platforms, such as mRNA and viral vectors

2. Supporting innovation in the vaccine development model

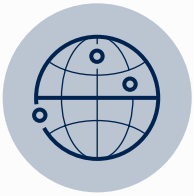
- Deploying novel clinical study designs that combined different trial phases into one trial to accelerate enrolment and data collection and reduce setup times
- Conducting parallel process development, scale up and technology transfer activities, and initiating commercial scale manufacturing activities at risk

3. Using operational excellence to accelerate development and manufacturing

- Utilising advanced data and analytics to enable rapid study set-up, real-time monitoring and data-sharing
- Optimising operational activities and decision-making processes to reduce 'white space' between critical activities and enable faster at-risk decision making

4. Promoting collaboration among stakeholders

- Driving collaboration amongst a range of stakeholders across governments, academia, industry, philanthropic and civil society organizations to provide an end-to-end approach from vaccine discovery through to roll-out
- Deploying platform trials, such as WHO Solidarity, to facilitate simultaneous and comparative assessment of the benefits and risks of multiple different vaccine candidates



5. Enabling continuous generation and review of evidence to support rapid approval

- Encouraging innovative regulatory approaches, including novel study designs, utilisation of platform data, and digitisation of review and submission processes
- Building on collaboration between regulatory agencies to align on preclinical and clinical standards, approaches, protocol temples and data structures to facilitate multi-country approvals

1 It is recognised that other vaccines for COVID-19 beyond the scope of this research exercise have since, or will, achieve WHO EUL.

Optimising deployment of existing innovations – what is already achievable

Analysis of the findings from this exercise indicate that combining the currently available innovations and best practices across vaccine developers could compress development timelines to approximately 250-300 days, approximately a 15-25% improvement over the fastest COVID-19 vaccines. Importantly, this assumes a pandemic where there was experience developing vaccines for a related pathogen on a rapid response platform already in use or under development, and an ongoing requirement for completion of Phase III clinical trials prior to emergency use authorisation (i.e., in a similar context to COVID-19).

Further accelerating vaccine development – a paradigm shift

Combining the currently available innovations and best practices across vaccine development into a fully optimised, integrated timeline to achieve vaccine approval by a stringent regulatory authority in approximately 250 days would indeed represent a significant achievement. However, this research and analysis also identified opportunities to accelerate beyond this timeline, including potentially achieving the 100-day aspiration where future pandemic circumstances necessitate it. This, however, would require a shift beyond the current vaccine development paradigm.

At the heart of the new paradigm is a fundamental shift towards preparedness. This will confer the capacity for rapid reaction to an identified outbreak and provide mechanisms for vaccine roll-out to targeted, high impact groups where there is early positive benefit-risk profile, while continuing in parallel to amass clinical evidence and larger volumes of vaccine doses for broader roll-out to larger populations. This shift towards preparedness would need to be a global effort with appropriate attention in both higher-and lower-income settings.

Such a paradigm would come with existing and new operational and clinical risks which would need to be extensively evaluated in advance of a pandemic, and should be pursued only if the right safeguards, particularly regarding safety risks, are put in place. Therefore, the paradigm shift can only be deployed in a future pandemic situation if the scientific progress between now and then has sufficiently progressed to eliminate the most material of these risks and regulatory practices and pathways have been modified accordingly.

This research exercise identified a number of key scientific and technological prerequisites that could underpin this paradigm shift: the first prerequisite is the ability to develop a pathogen-specific vaccine during an outbreak by adapting **previously developed and well-characterised prototype vaccines** against closely related viruses; the second prerequisite is the availability and readiness of **global clinical trial infrastructure, standards and tools**; the third prerequisite is the ability to develop and use **more rapid measures of vaccine-induced immune response and protection** thereby shortening the time to determine trial outcomes; the fourth prerequisite is an ability to **rapidly manufacture and validate the first batch of experimental vaccines** that are suitable for human use; the fifth prerequisite is the ability for **early characterisation of the outbreak and pathogen**.

Key scientific and technological prerequisites underpinning a fundamental shift towards preparedness

1. Pre-existing prototype vaccines for representative pathogens across multiple virus families

- Create libraries of vaccine constructs against representative pathogens from virus families with greatest pandemic potential
- Build significant platform experience that could be leveraged for rapid adaptation in an outbreak

2. Global clinical trial infrastructure and readiness

- Establish global clinical trials networks with pre-established processes and protocols to enable rapid generation of clinical evidence of efficacy and safety
- Supported by a global clinical laboratory network to facilitate faster data readouts

3. Earlier biomarkers of robust immune response and protection

- Identify immune markers that provide an indication of vaccine efficacy prior to the traditional 14–21-day timeline taken to observe a full immune response
- Utilise *in silico* modelling to identify correlates of protection and assess potential toxicity

4. Global capacity for rapid manufacture and validation of experimental vaccines

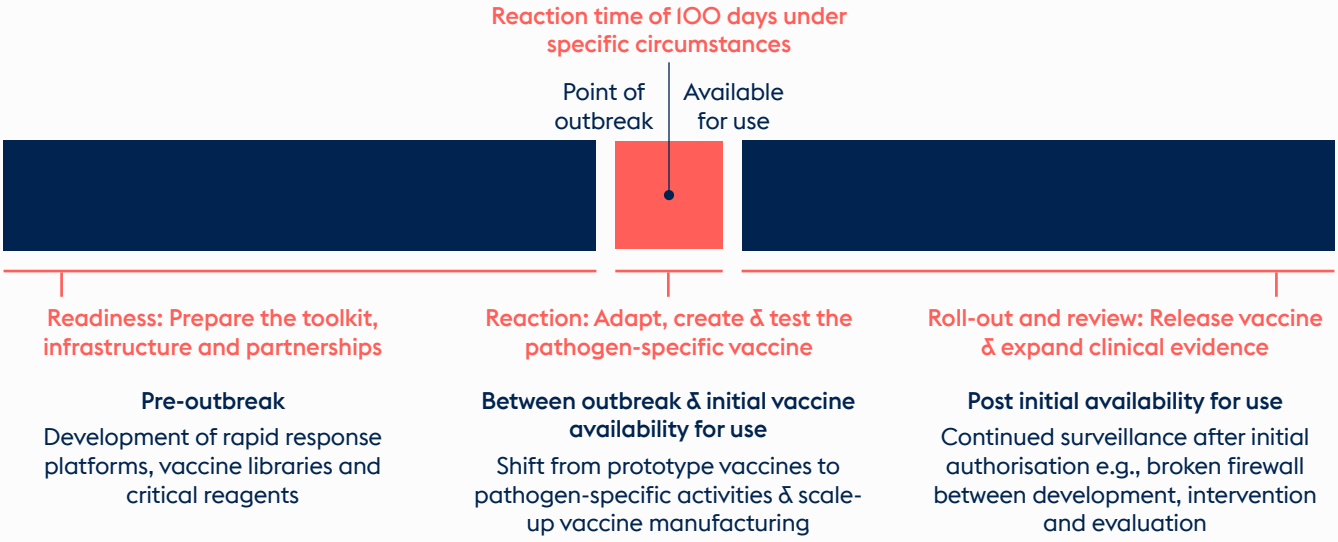
- Optimise manufacturing processes for rapid initial production and subsequent scaling
- Maintain a network of 'warm' manufacturing facilities and reserved capacity for multiple different platforms that could be activated within days

5. Global capabilities for early characterisation of pathogens and outbreaks

- Strengthen active, continuous global surveillance capabilities to enable faster alert triggers, especially in lower-income regions
- Harmonise global approaches for sequence sharing and criteria for triggering a global alert

Investment in initiatives to achieve these prerequisites pre-outbreak could provide a level of readiness that opens up the ability to react within 100 days. Under emergency circumstances, vaccine development in response to a new outbreak would then consist of the adaptation of well-understood prototype vaccine candidates into a new pathogen-specific vaccine (circa *5 weeks*), immediate testing in a rapidly expanding trial population (circa *8 weeks*), and emergency approval for use in the populations with the highest risk profile once the immunogenicity of the pathogen-specific vaccine has been documented but before event-derived efficacy is available (circa *1 week*). Evidence generation, including the collection of efficacy data based on the accumulation of events or gathering real world effectiveness data based on an early deployment, would continue after the first emergency use authorisation as part of an ongoing roll-out and review, and support staggered approval for use in broader populations and lower risk groups.

A new paradigm for vaccine development for outbreak response



An enabling policy and financing context

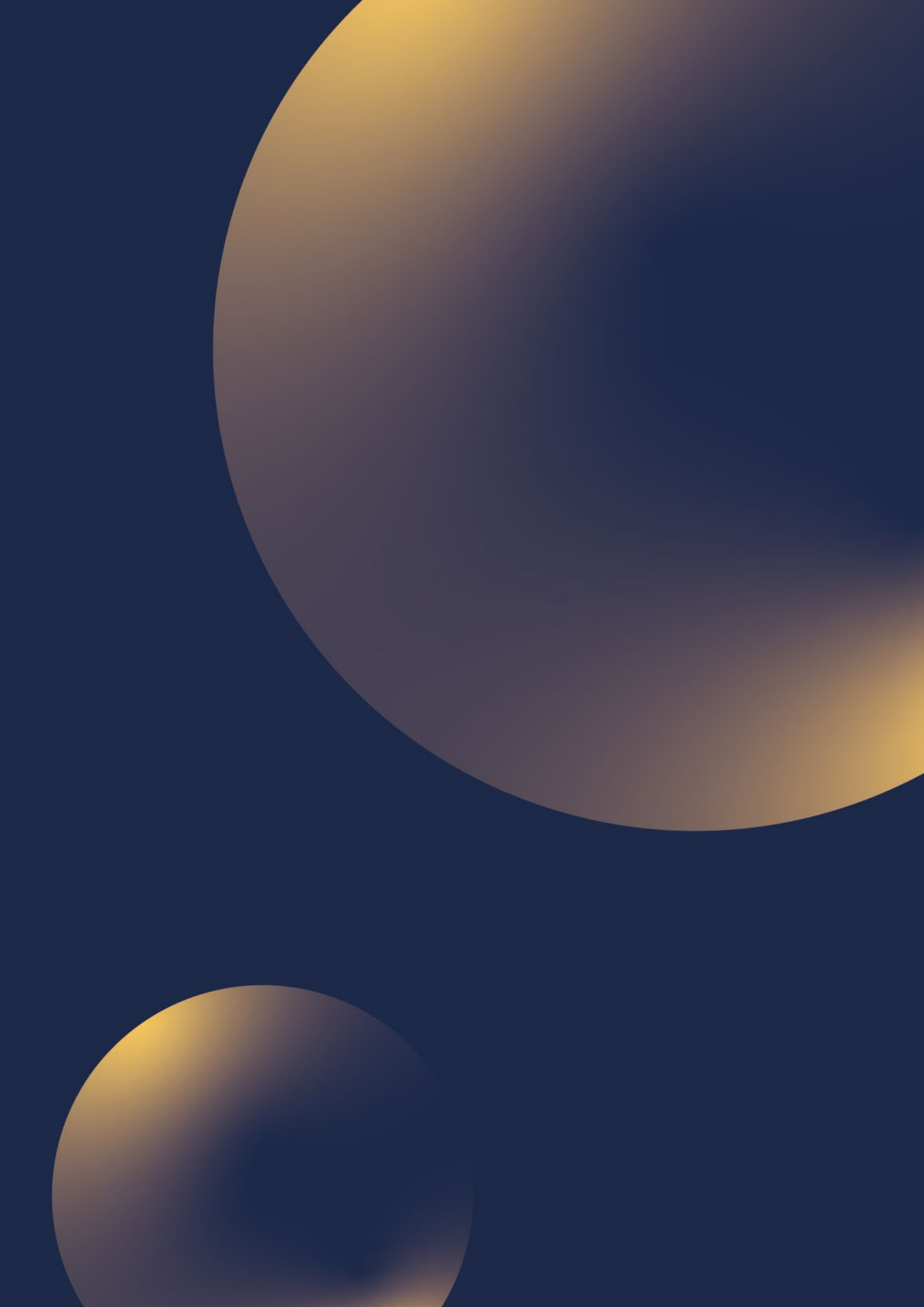
Many of the challenges to implementing the scientific and technological innovations identified from this research relate to the policy and financing architecture for epidemic and pandemic preparedness and response. The response to the COVID-19 pandemic benefitted from regulatory collaboration and pragmatism, which enabled preclinical and human trials to be conducted simultaneously based on previous data generated from within the same technology platform, clear articulation of criteria for safety and efficacy, the employment of non-traditional trial designs, and rolling review of regulatory dossiers. In preparation for the next pandemic, further innovations could include relatively straightforward changes such as a detailed globally harmonised template for regulatory dossiers, potentially based on improvements to the existing Common Technical Document, and advanced benefit-risk assessment methodologies to provide additional guidance regarding the data needed to support emergency authorisation or approval. Other innovations that would help – such as the assessment of the role *in silico* modelling can play in the analysis of benefit and risk, the creation of robust criteria and approaches to authorise vaccine use on the basis of immunogenicity data, and the agreement on the circumstances under which this is warranted – present harder challenges.

More generally the global response to COVID-19 exposed the fragmented and uncoordinated nature of the current global preparedness and response architecture for emerging infectious diseases of outbreak, epidemic and pandemic potential. Lack of coordination and clarity of roles, absence of established surge financing mechanisms for R&D and at-risk manufacturing and procurement, and lack of mechanisms to enable global access to vaccines, diagnostics, therapeutics and critical equipment, has resulted in significant delays in vaccine manufacturing and highly inequitable access to vaccines. An accelerated development timeline risks making these challenges even more significant, therefore addressing critical policy and financing issues will be key to enable a functioning, agile and networked global ecosystem capable of delivering the 100-day aspiration.

Call to action

Stopping or preventing the next pandemic, let alone in 100 days, is not something a single country or organisation can do alone. Nor will it likely be achieved by simply funding vaccine developers and biotech companies to advance innovative work. Success will require advancements in organisation, governance, and financing of global preparedness systems, and multiple, interconnected scientifically guided collaborative efforts. The 'moonshot' goal of making a vaccine against a new pandemic pathogen in 100 days is ambitious, but this research exercise shows it is not impossible.

Several organisations, including CEPI have laid out ambitious programmes leveraging many of the approaches described in this paper. Other countries and regions have begun additional activities such as expanding vaccine manufacturing so that ready, prepositioned manufacturing capacity is less likely to be a limiting step in responding to the next pandemic.



Contents

Introduction

Vaccines are at the heart of how modern societies counter infectious disease threats. They are among the world's most potent tool against pandemic risks and are critical to future public health responses to outbreaks. The faster an effective vaccine is developed and deployed, the faster a potential pandemic threat can be contained and controlled if it is used. The ability to contain pandemic threats must have a global focus with appropriate attention in both higher- and lower-income settings, particularly given the latter are where new infections, including the next Disease X, are most likely to emerge[2].

The development and authorisation of novel vaccines against SARS-CoV-2 in less than a year is a triumph of scientific and technological innovation. Three different vaccines received emergency authorisation from a stringent regulatory authority[3] within a year of the viral sequence becoming available on 11 January 2020, with the first vaccine, BNT162b2 from Pfizer-BioNTech, taking just 326 days. This represents a step-change from traditional vaccine development timelines, driven by the extent of the human and economic damage created by the devastating nature of the pandemic, and capitalizing upon numerous innovations arising from decades of previous research and development on coronaviruses and innovative vaccine platforms.

However, despite these accelerated development timelines, more than 65 million COVID-19 cases and 1.6 million resulting deaths were recorded worldwide before BNT162b2 received authorisation for emergency use[4], by which point the pandemic had become unstoppable. A more rapid response that contained the spread of the virus could have significantly limited the human and socio-economic cost of the pandemic: an estimated US$28 trillion lost in the period 2020-2025 – the deepest shock to the global economy since the Great Depression of 1929-39[5]; 90% of schoolchildren unable to attend school at the highest point in 2020[6]; an increase in gender-based violence[7]; and as many as 150 million people pushed into extreme poverty by 2021– with a disproportionate impact on low- and lower middle-income countries (LICs and LMICs)[8]. It is therefore paramount to identify opportunities to further accelerate vaccine development responses to future pandemic threats.

In recognition of the potential impact that earlier, widespread availability of vaccines could have, CEPI has articulated an aspirational goal: ***vaccines should be ready for initial authorisation and manufacturing at scale within 100 days of recognition of a pandemic pathogen, when appropriate***. Coupled with improved surveillance providing earlier detection and warning, and with swift and effective use of non-pharmaceutical interventions such as testing, contact tracing and social distancing to suppress disease transmission, delivering a vaccine within 100 days would give the world a better chance of containing and controlling future pathogenic threats and averting the type of catastrophic global public health and socio-economic impacts caused by COVID-19. These efforts should have a strong focus on increasing capabilities in LICs and LMICs and enabling equitable access to products once developed – no one is safe until everyone is safe.

2 Allen, T. et al., 2017. Global hotspots and correlates of emerging zoonotic diseases. Nature Communications, p. 8:1124.

3 The concept of a stringent regulatory authority or SRA was developed by the WHO Secretariat and the Global Fund to Fight AIDS, Tuberculosis and Malaria to guide medicine procurement decisions and is now widely recognized by the international regulatory and procurement community. A list of stringent regulatory authorities can be consulted on: https://www.who.int/initiatives/who-listed-authority-reg-authorities/SRAs

4 WHO, 2022. WHO Coronavirus (COVID-19) Dashboard.

5 Gopinath, G., 2020. A Long, Uneven and Uncertain Ascent.

6 UNESCO, 2021. UNESCO figures show two thirds of an academic year lost on average worldwide due to Covid-19 school closures.

7 UNWOMEN, 2022. Facts and figures: Ending violence against women.

8 The World Bank, 2020. COVID-19 to Add as Many as 150 Million Extreme Poor by 2021.

This 'moonshot' goal has been widely adopted by governments around the world, with specific endorsement in the Carbis Bay G7 Summit Communiqué (UK 2021)[9], in the G20 Rome Leaders' Declaration (Italy 2021)[10], and by the US government[11]. Several vaccine developers have also started exploring strategies for achieving this aim[12]. Understanding and capitalising upon the opportunities presented by a wide range of innovations – across research, manufacturing, regulation and distribution, and underpinned by enhanced coordination and routes to finance – is a critical component of this effort. This is because planning for what is possible in the future is grounded in what has already been shown to be possible right now.

CEPI has undertaken an in-depth exercise to identify innovations that could accelerate the development process and challenges that would need to be overcome to meet the 100-day aspiration. This analysis draws on joint research carried out between CEPI and McKinsey & Company, which included interviews with 46 representatives from vaccine-development firms, international organisations, regulatory agencies, academia, and the media, along with an extensive review and analysis of publicly available information (including scientific publications, lessons learnt exercises, formal reports and company announcements)[13].

This paper describes the findings of this exercise, focusing on the factors that enabled such rapid development of COVID-19 vaccines to develop a consensus around the most condensed timeline under which vaccines could be developed if these lessons were applied. It then describes a substantial shift from the current vaccine development paradigm necessary to deliver a vaccine for initial use within 100 days, and highlights areas of scientific and technological advancement that could underpin this shift. Recognising that innovations in research and development can only deliver global, real-world impact if they are made equitably accessible and are implemented in a supportive financing and governance ecosystem, the paper then discusses the requirements of an effective enabling pandemic preparedness and response ecosystem. Finally, the paper describes the investments and activities that CEPI and others are undertaking towards achieving the 100-day aspiration.

This paper focuses very deliberately on the technical and scientific innovations in vaccine development required to achieve speed in responding to an outbreak. This focus on speed should not distract from the importance of achieving scalability of manufacturing and ensuring equitable access to all in need of being protected during an outbreak, regardless of geographic location or ability to pay. Just as is the case with the 100-day aspiration, the ability to deploy vaccines at scale and ensure equitable access requires a shift in the current paradigm, prepositioning investments, processes and partnerships and being prepared to react on day one of a potential pandemic outbreak. Several organisations have made recommendations towards achieving the complementary and vital objectives of scale and access, including the Center for Global Development in their call for the 'second 100 days mission' (i.e., within 100-200 days from identification of a pandemic threat). The 'second 100 days mission' builds on the 100-day aspiration towards a coordinated strategy to ensure speed, equitable and at scale manufacturing, procurement and deployment of medical countermeasures in the wake of pandemic risk[14].

Finally, the focus on speed, scale and access in developing vaccines should not distract from the need to improve global approaches to epidemic and pandemic response through the deployment of appropriate countermeasures, including non-pharmaceutical interventions. Most importantly, national investments towards preparedness and health systems strengthening are important building blocks towards a world better protected against the human, social and economic impact of outbreaks of infectious diseases.

9 The Group of Seven, 2021. Carbis Bay G7 Summit Communique.

10 G20 Leaders, 2021. G20 Rome Leaders' Declaration.

11 The White House, 2021. American Pandemic Preparedness: Transforming Our Capabilities.

12 Kimball, S., 2021. Moderna CEO says it will take months to clear a new Covid vaccine targeting omicron.

13 See Appendix I for a full overview of the methodology

14 Glassman, A., Guzman, J., Kaufman, J. & Yadav, P., 2022. Rapid and Equitable Access to Medical Countermeasures: Lessons, Landscape, and Near-Term Recommendations, Washington, DC: Center for Global Development.

Accelerated vaccine development during the COVID-19 pandemic

To understand the factors that enabled accelerated vaccine development during the COVID-19 pandemic, this exercise evaluated the development and authorisation timelines of COVID-19 vaccine candidates that, as of October 2021, were either approved by a stringent regulatory authority or issued with an EUL by the WHO (AstraZeneca/Serum Institute of India, Bharat Biotech, CanSino Biologics, Gamaleya Research Institute, Johnson & Johnson, Moderna, Novavax/Serum Institute of India, Pfizer-BioNTech, Sinopharm, Sinovac).

As shown in Table 1, the development timelines from the day the COVID-19 sequence was made available until emergency use authorisation by a stringent regulatory authority or WHO EUL ranged from 326 to 706 days for the vaccines evaluated in this exercise[15]. Inactivated and mRNA vaccines started to reach late-stage clinical trials in July 2020, followed two months later by several viral vector and one subunit vaccine. The first vaccines to receive approval by a stringent regulatory authority were the mRNA vaccines developed by Pfizer-BioNTech and by Moderna and the viral vectored vaccine developed by AstraZeneca. The development of the viral vectored vaccine by Gamaleya and the inactivated vaccines by Sinopharm and Sinovac proceeded in parallel and achieved faster emergency use authorisations, but only in the country where they were developed and based solely on safety and immunogenicity data (i.e., without an interim Phase III event-based efficacy readout). Sinopharm and Sinovac achieved EUL 10 months after national approval[16] EUL was still pending for the Gamaleya vaccine as of October 2022.

Figure 1 illustrates how the first authorised COVID-19 vaccines were developed five- to ten-times faster when compared with the development timelines of a reference set of historic vaccines[17].
This was largely because Phase III clinical trials were conducted rapidly (approximately four months for the first stringent regulatory authority-approved COVID-19 vaccines versus 26-48 months for typical Phase III studies), and the time for regulatory filing, review and approval was very short (less than a month for COVID-19 vaccines versus 12 months for other vaccines).

15 It is recognised that other vaccines for COVID-19 beyond the scope of this research exercise have since, or will achieve WHO EUL.

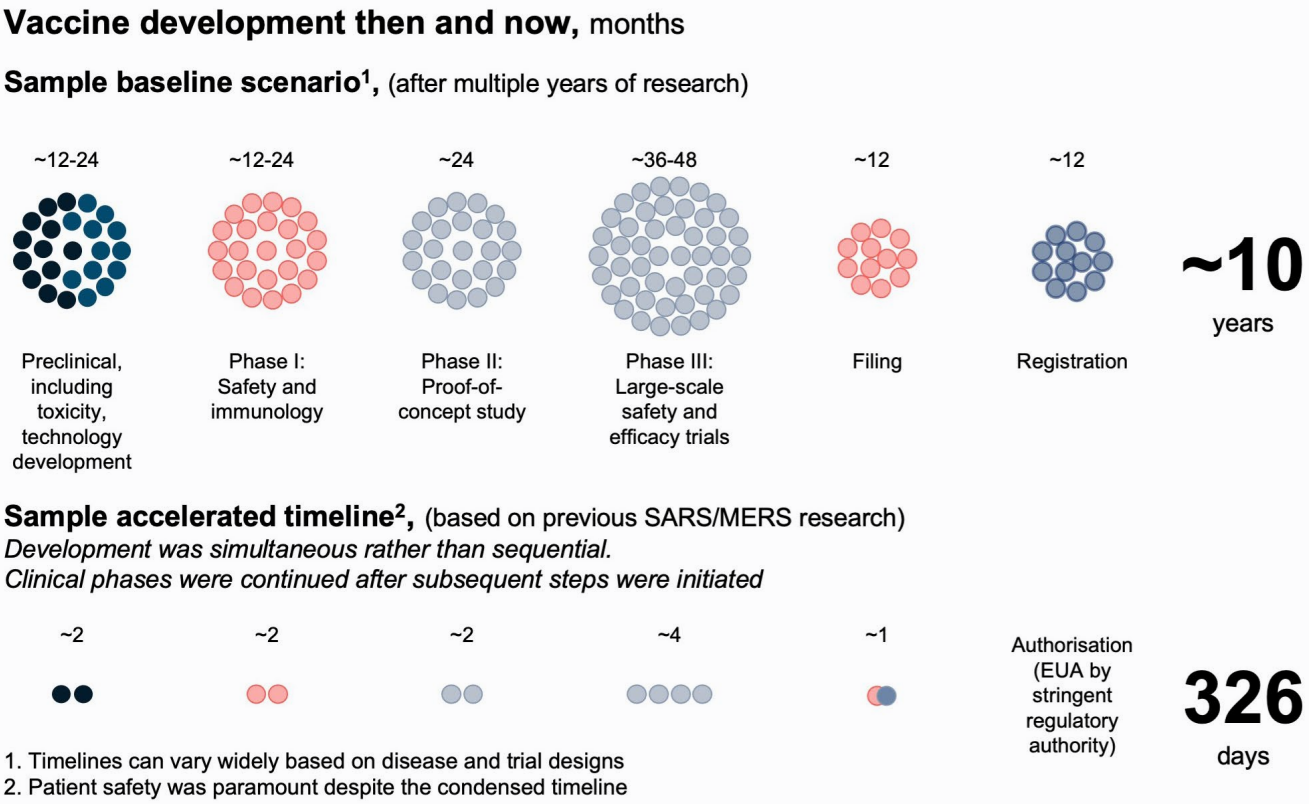
16 WHO, 2022. COVID-19 Vaccines with WHO Emergency Use Listing.

17 Recombinant zoster vaccine for herpes zoster (Shingrix); 9-valent HPV vaccine for human papilloma virus (Gardasil 9); pneumococcal 7-valent conjugate vaccine (Prevnar septavalent) for pneumococcal infections; and Ebola Zaire vaccine (Ervebo) for Ebola virus disease

Table 1: Development timelines of COVID-19 vaccines approved by stringent regulatory authorities or with EUL (data accurate as of 16 January 2022)

Developer	Vaccine	Platform	First-in-human start	Phase III start	First (conditional) approval or emergency use (country)	Earliest SRA approval or EUL (by WHO)	Days from sequence availability until earliest SRA approval / emergency use or EUL
AstraZeneca/ Serum Institute of India	Vaxzevria®/ Covishield® (AZD1222)	Viral vector	04/23/2020	05/28/2020 (Phase II/III)	12/30/2020 (UK)	12/30/2020 (UK) / 02/15/2021 (WHO)	354
Bharat Biotech	Covaxin® (BBV152)	Inactivated	07/15/2020	11/11/2020	01/02/2021 (India)	11/03/2021 (WHO)	662
CanSino Biologics	Convidecia™ (Ad5-nCoV)	Viral vector	03/16/2020	09/15/2020	25/02/2021 (China)	03/22/2021 (Hungary)	436
Gamaleya Research Institute	Sputnik V (Gam-COVID-Vac)	Viral vector	06/17/2020	09/07/2020	08/11/2020 (Russia)	01/21/2021 (Hungary)	376
Johnson & Johnson	COVID-19 Vaccine Janssen (Ad26. COV2.S)	Viral vector	07/22/2020	09/07/2020	02/27/2021 (US)	02/27/2021 (US)	413
Moderna	Spikevax® (mRNA-1273)	mRNA	03/16/2020	07/27/2020	12/18/2020 (US)	12/18/2020 (US)	342
Novavax/ Serum Institute of India	Nuvaxovid®/ Covovax® (NVX-CoV2373)	Subunit	05/25/2020	09/24/2020	11/01/2021 (Indonesia)	12/17/2021 / 12/20/2021 (WHO)	706
Pfizer-BioNTech	Comirnaty® (BNT162b2)	mRNA	04/23/2020	07/27/2020	12/02/2020 (UK)	12/02/2020 (UK)	326
Sinopharm	Covilo® (BBIBP-CorV)	Inactivated	04/12/2020	07/15/2020	07/22/2020 (China)	05/07/2021 (WHO)	482
Sinovac	CoronaVac®	Inactivated	04/16/2020	07/21/2020	08/29/2020 (China)	06/01/2021 (WHO)	507

Figure I: Development stages and timelines for vaccine development and authorisation



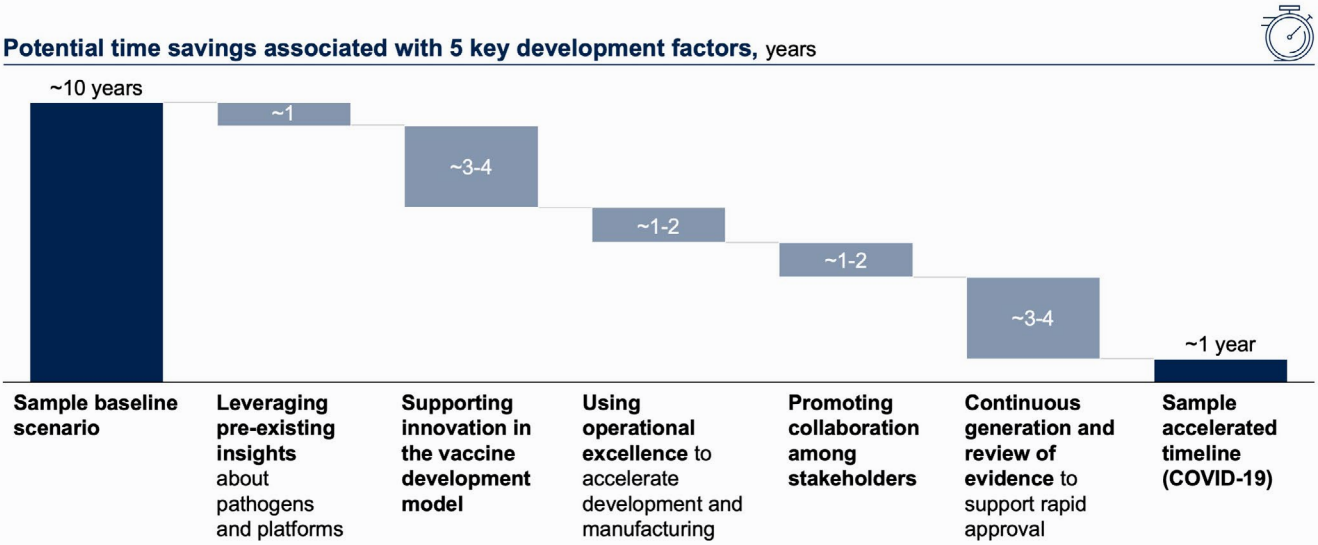
A 2022 report by the Wellcome Trust[18] identified four major factors responsible for the accelerated development and authorisation of COVID-19 vaccines: **the pandemic context** which inspired strong political will and a pressure to act that increased the risk appetite for key stakeholders; **the unprecedented financial investment** into the response which enabled at risk-investments and advance purchase agreements supporting all stages of the vaccine development research and development process; **a proactive and pragmatic regulatory approach** which prioritised human resources resulting in increased collaboration with developers, and provided more flexibility in the timing of data requirements and review processes; and **faster clinical development** supported by decades of previous research and development on innovative vaccine platforms, coronaviruses, and structural biology of protein antigens; which coupled with the aforementioned three factors enabled rapid decision making and the ability to conduct clinical trial phases in parallel rather than sequentially.

The findings of the current research exercise align with those of the Wellcome Trust report, identifying a catalogue of 37 innovations[19] that contributed to accelerated development, early manufacturing and authorisation of COVID-19 vaccines. These innovations can be categorised into five broad areas and are underpinned by three core principles: prior knowledge available for deployment; multiple processes running wholly or partly in parallel; and significant collaboration between stakeholders globally. Figure 2 illustrates the extent to which each of the five areas of innovation contributed to acceleration of vaccine development during the COVID-19 pandemic, with each area discussed in more detail below.

18 Wellcome Trust, 2022. COVID-19 Vaccines: The Factors that Enabled Unprecedented Timelines for Clinical Development and Regulatory Authorisation, London: Wellcome Trust.

19 See Appendix III for the catalogue of innovations that could accelerate vaccine development timelines, including 37 innovations that directly contributed to accelerated development of COVID-19 vaccines.

Figure 2: Summary of the impact of each of the five areas of innovation on COVID-19 vaccine development timelines



Note: Time savings across acceleration categories are not cumulative and depend on critical development path

I. Leveraging pre-existing insights about pathogens and platforms

Although SARS-CoV-2 was a novel pathogen, initial vaccine development efforts were greatly informed by experience gained from previous outbreaks of pathogens within the same virus family, including SARS-CoV-1 and Middle East Respiratory Syndrome-related coronavirus (MERS-CoV)[20]. These previous experiences yielded information that enabled the rapid design of vaccines that elicit strong immune responses against the spike protein of SARS-CoV-2, for example by enabling stabilisation of the spike protein in the prefusion form.

COVID-19 vaccine development also benefited from significant previous investments in novel rapid response vaccine platforms such as mRNA and viral vectors, with a high ease of modification for new antigens. For example, prior to the pandemic, CEPI had already committed to invest up to US$19 million in non-clinical and early clinical development of the University of Oxford's ChAdOx1 platform for Nipah virus, Lassa Fever virus and MERS-CoV, while in 2016, the US Government's Biomedical Advanced Research and Development Authority (BARDA) awarded up to US$125 million to Moderna for development of mRNA vaccines for Zika virus[21]. Moderna were able to leverage their knowledge and previously generated non-clinical toxicology and nonhuman primate data from research into MERS, Zika and other viruses[22] to produce the first batches of mRNA-1273 just 42 days after the SARS-CoV-2 sequence was released, and commence first-in-human studies three weeks later, 63 days after sequence identification[23].

20 Corbett, K.S. et al., 2020. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. Nature 586, 567–571.
21 Moderna, 2022. Strategic Partnerships.
22 American Chemical Society, 2020. The tiny tweak behind COVID-19 vaccines.
23 Hodgson, J., 2020. The pandemic pipeline.

2. Supporting innovation in the vaccine development model

Rapid vaccine development requires taking risks. The current vaccine development model (Figure 1) comprises sequential stages of preclinical development, Phase I (basic safety and immunology), Phase II (proof-of-concept studies), Phase III (large-scale safety and efficacy trials), followed by filing and registration. In parallel, manufacturing processes need to be developed, scaled-up and prepared for filing.

Traditionally, none of these stages take much less than a year, with this research exercise indicating that late-stage trials typically take between three and four years. Moreover, the sequential nature of the traditional development model, designed to mitigate the significant financial risk associated with vaccine development, often results in bottlenecks that add to overall development timelines. Given the nature of the pandemic, an unprecedented level of financial investment was made available for COVID-19 vaccine development enabling each of these stages to be undertaken at great pace, and crucially, in parallel.

Many developers deployed clinical study designs that combined different trial phases into one trial to accelerate enrolment and data collection and reduce setup times. For example, Pfizer-BioNTech tested multiple candidates in parallel at different dose ranges to determine the lead to take forward into Phase II/III within 13 weeks[24], whereas Moderna tested its vaccine in separate Phase I and II trials, taking a combined 19 weeks until the beginning of Phase III[25,26]. Pfizer–BioNTech also achieved rapid enrolment of patients by deploying a merged Phase II/III design and leveraging its global-site network, including a longstanding strategic partnership with clinical research organisation, ICON, resulting in 30,000 patients enrolled by day 54 of the study[27].

On the manufacturing side, pre-optimisation of manufacturing processes enabled accelerated availability of clinical supply. For example, BioNTech was able to rapidly adapt its in-house clinical manufacturing capabilities (originally established to produce candidates for oncology indications)[28] to generate first experimental batches of vaccine candidate for clinical use within one week, compared to several months in more typical circumstances[29]. Meanwhile, many developers undertook parallel process development, scale-up and technology transfer activities, and began commercial scale manufacturing activities at risk. For example, AstraZeneca signed initial manufacturing and technology transfer agreements as early as April 2020 when AZD1222 was still in early clinical development[30], in parallel to adapting assays and processes and scaling up manufacturing capacity in its own facilities. Commercial scale manufacturing began in early summer 2020 at risk, while Phase II studies were ongoing and approval of the vaccine still highly uncertain[31]. AstraZeneca also recruited multiple manufacturing partners and signed several supply contracts with governments and organisations in this period.

24 Anderson, A. 2022. A lightspeed approach to pandemic drug development.
25 ClinicalTrials.gov, 2020. Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) for Prophylaxis of SARS-CoV-2 Infection (COVID-19).
26 ClinicalTrials.gov, 2020. A Study to Evaluate Efficacy, Safety, and Immunogenicity of mRNA-1273 Vaccine in Adults Aged 18 Years and Older to Prevent COVID-19.
27 Pfizer, 2020. Pfizer and BioNTech Propose Expansion of Pivotal COVID-19 Vaccine Trial.
28 National Cancer Institute, 2020. Can mRNA Vaccines Help Treat Cancer?
29 BioNTech, n.d. mRNA Vaccines.
30 AstraZeneca, 2020. AstraZeneca and Oxford University announce landmark agreement for COVID-19 vaccine.
31 Catalent, 2020. Catalent Signs Agreement with AstraZeneca to Manufacture COVID-19 Vaccine Candidate.

3. Using operational excellence to accelerate development and manufacturing processes

As well as conducting defined stages of vaccine development in parallel, vaccine developers were also able to realise significant timeline gains by optimising operational activities and decision-making processes within and between stages.

A number of approaches to accelerate operational processes involved the use of advanced data and analytics. These included predictive epidemiological methods to help clinical study site selection teams and clinical networks mobilise quickly in prime geographical locations with peak cases to prepare for evidence generation. For example, AstraZeneca included countries in its Phase III trial based on current and predicted epidemiological data of COVID-19 cases, conducting late-stage trials in South Africa and Brazil due to low caseloads in the Northern Hemisphere at the time and predicted increased case developments in the selected geographies. They also leveraged existing clinical trial networks for fast site activation to accelerate patient recruitment in the first Phase III trial for COVID-19 in Latin America[32].

Other analytics-enabled approaches that yielded significant time-savings included real-time monitoring and transmission of operational parameters that influence trial timelines (e.g., recruitment, visits and dropout rates) and/or clinical measures and outcomes that impact endpoint decision (e.g., attack rates, vaccine efficiencies and safety events). Pfizer utilised real-time monitoring to enable rolling submission and continuous review of new data by the UK Medicines and Healthcare products Regulatory Agency (MHRA), allowing the regulatory dossier to be compiled in parallel with trial execution[33]. Pfizer also deployed AI-enabled real-time automated data cleaning processes to achieve database-lock within 22 hours after last case entries (compared to a typical timeframe of 3-6 weeks)[34], enabling full submission of the dossier to be achieved within one week after study completion[35,36].

Developers also employed a variety of approaches to reduce 'white space' – i.e., time taken between operational activities, such as handovers between functions or governance review cycles – and enable faster at-risk decision making across all stages of development. The research and analysis identified that approximately 12 months of traditional vaccine development 'white space' was compressed to less than three weeks during COVID-19 through approaches such as eliminating layers of organisational hierarchy and placing decision-making authority with expert functions; empowering teams to make at-risk go/no go decisions based on incomplete data; and ensuring direct access to executive decision-makers where needed. For example, Moderna adopted a decentralised organisational model that gave specific teams decision-making rights and the independence to move quickly, while daily stand-up working meetings were held with the CEO to facilitate overall progress. Pfizer also set up similar check-in and rapid decision-making processes[37].

Many developers also implemented 24/7 operations in both manufacturing and clinical development activities to increase productivity and accelerate timelines. For example, in April 2020 Moderna announced plans to hire up to 150 new employees, including skilled manufacturing staff to scale operations from two shifts per day, 5 days per week to three shifts per day, 7 days per week[38].

32 ClinicalTrials.gov, 2020. Phase III Double-blind, Placebo-controlled Study of AZD1222 for the Prevention of COVID-19 in Adults

33 Medicines & Healthcare products Regulatory Agency, 2021. Freedom of Information request on the expedited rolling review for temporary authorisations of the Pfizer/BioNTech, Oxford/AstraZeneca and Moderna vaccines (FOI 21-747).

34 Pfizer, 2022. How a Novel 'Incubation Sandbox' Helped Speed Up Data Analysis in Pfizer's COVID-19 Vaccine Trial.

35 Pfizer, 2020. Pfizer and BioNTech Conclude Phase 3 Study of COVID-19 Vaccine Candidate, Meeting All Primary Efficacy Endpoints.

36 US FDA, 2020. Emergency Use Authorization for Pfizer-BioNTech COVID-19 Vaccine Review Memo.

37 Anderson, A. 2022. A lightspeed approach to pandemic drug development.

38 Bloomberg, 2020. Moderna Announces Award from U.S. Government Agency BARDA for up to $483 Million to Accelerate Development of mRNA Vaccine (mRNA).

4. Promoting collaboration among stakeholders

A key accelerator of vaccine development timelines for COVID-19 was the unprecedented level of global collaboration amongst a range of stakeholders across governments, academia, industry, philanthropic and civil society organisations. These collaborations were critical in creating the financing environment to enable at-risk vaccine development and manufacture at scale, bringing together innovative vaccine platforms with large scale manufacturing and supply expertise, matching global demand for vaccine production capacity with available supply and aligning global R&D, manufacturing, procurement, distribution and deployment activities to minimise lead times until vaccine availability.

One notable example is COVAX, the partnership between CEPI, Gavi the Vaccine Alliance, WHO and UNICEF, designed to accelerate development and manufacture of COVID-19 vaccines, and to secure fair and equitable access. COVAX was established on the basis of aligning roles, responsibilities, capabilities and equitable access principles to enable efficient collaboration, increase impact and ensure rapid coordination across key disciplines including regulatory, financing, infrastructure, clinical development, manufacturing and supply. COVAX invested in a diverse portfolio of COVID-19 vaccines, providing at-risk financing for R&D, manufacturing and procurement to deliver sufficient vaccine globally to enable countries to cover the most vulnerable 20% of their populations. At the date of this report, more than 1.84 billion doses of vaccine had been delivered to 146 countries through COVAX[39]. However, COVAX faced numerous challenges including insufficient initial funding to secure early vaccine doses, export bans affecting manufacturers, and difficulties in scale-up of production; therefore despite these efforts, access to life-saving vaccines for the poorest countries lagged behind their wealthier counterparts, highlighting the need for greater focus on ensuring fair equitable allocation of vaccines globally.

Meanwhile collaborative efforts between industry manufacturers provided opportunities to leverage available manufacturing capacity to accelerate global supply and access to COVID-19 vaccines. For example, Serum Institute of India partnered with both Novavax and AstraZeneca to supply vaccines to the Indian government and a large number of low- and middle-income countries[40,41], while Sanofi, in addition to advancing in-house COVID-19 vaccine programmes, also entered into manufacturing and supply agreements to use its manufacturing network to support increased production of both Pfizer-BioNTech and Johnson & Johnson COVID-19 vaccines[42]. While these partnerships were formally established at or shortly after emergency authorisation of these vaccines, they exemplify the potential for industry collaboration to accelerate global supply by alleviating regional and global capacity constraints.

39 UNICEF Supply Division, 2022. COVID-19 Vaccine Market Dashboard.

40 Serum Institute of India PVT. LTD., 2021. Serum Institute of India and Novavax Receive Emergency Use Authorization in India for COVOVAX™.

41 AstraZeneca, 2021. Serum Institute of India obtains emergency use authorisation in India for AstraZeneca's COVID-19 vaccine.

42 Sanofi, 2021. Sanofi to provide manufacturing support to Johnson & Johnson for their COVID-19 vaccine to help address global supply demands.

5. Continuous generation and review of evidence to support rapid approval

The first COVID-19 vaccines were authorised under accelerated emergency and/or conditional use procedures on the basis of interim data and smaller numbers of accrued cases. This allowed broad-based vaccination programmes to be initiated while full licensure was pursued in parallel, justified by the benefit-risk profile of the vaccine and disease. Accelerated authorisation for COVID-19 vaccines was enabled by a number of innovative regulatory approaches across many aspects of vaccine development, including non-traditional study designs, utilisation of platform data, and digitisation of review and submission processes; and involving effective collaboration between regulatory agencies and vaccine developers.

The use of seamless and adaptive study designs to streamline and accelerate the COVID-19 vaccine development pathway required a high degree of regulatory flexibility, for example to determine the most appropriate interim checkpoints and to allow for continual updating of clinical protocols. Use of digitally enabled and automated real-time data collection and monitoring permitted developers and regulators to conduct live interim analysis and adjust the design of clinical trials as they were conducted based upon pre-specified criteria. These technologies also enabled rapid regulatory review of full dossiers, as was the case for Pfizer–BioNTech vaccine which received emergency use authorisation from the US Food and Drug Administration (FDA) within three weeks after filing, and within 5 weeks after publication of interim Phase III results[43,44,45]. Regulatory agencies also implemented rolling reviews to allow continual submission of new data without predefined submission deadlines, further accelerating review timelines. For example, in October 2020, the European Medicines Agency (EMA) announced implementation of rolling reviews of the AstraZeneca candidate to evaluate data relating to effectiveness, safety and quality as it became available[46].

The use of safety data from previous experience of vaccine platforms also enabled acceleration of vaccine development timelines by allowing earlier decisions on vaccine safety based on limited but continuously updated clinical data. This approach allowed for expedited assessments of benefit-risk, and for conditional approval on the basis of pre-defined interim safety read-outs being achieved. The FDA provided nonbinding recommendations as guidance to industry for the emergency use authorisation (EUA) of COVID-19 vaccines in October 2020, which it updated several times[47]. This document provided recommendations regarding data and information needed to support issuance of an EUA, including guidance on continuing clinical trials following EUA to assess long-term safety.

Use of these innovative regulatory approaches to accelerate vaccine development and authorisation through emergency and/or conditional use procedures necessitated earlier, more frequent and more effective dialogue and engagement between developers and regulators. This allowed for closer alignment of requirements during study design and protocol development; faster feedback loops for real-time (and rolling) data reviews and improved planning for post-authorisation commitments. For example, AstraZeneca established continuous communication channels with a number of regulatory agencies, many with whom it had significant prior relationships with, including the MHRA and the EMA. Owing to previous experience of working closely with MHRA, AstraZeneca was highly familiar with submission templates, ways of working and technical requirements. This allowed MHRA to support fast data assessment and response times to questions, enabling rapid filing and approval of the AstraZeneca vaccine in the UK.

43 Pfizer, 2020. Pfizer and BioNTech to Submit Emergency Use Authorization Request Today to the U.S. FDA for COVID-19 Vaccine

44 FDA, 2022. Emergency Use Authorization.

45 Pfizer, 2020. Pfizer and BioNTech Announce Vaccine Candidate Against COVID-19 Achieved Success in First Interim Analysis from Phase 3 Study

46 European Medicines Agency, 2020. EMA starts first rolling review of a COVID-19 vaccine in the EU.

47 Krause & Gruber, 2020. Emergency Use Authorization of Covid Vaccines — Safety and Efficacy Follow-up Considerations. New England Journal of Medicine, p. e107(1-3).

Given the global reach of the pandemic, collaboration between regulatory agencies was a critical enabler of accelerated global vaccine development and authorisation. This included alignment on preclinical standards; development of harmonised clinical trial protocol templates that could be rapidly adapted by developers and used globally; ethics committee alignment; pre-approval of trial designs and dataset structures; and mechanisms for developer-consented information sharing between regulatory agencies to facilitate multi-country approvals. In November 2020, the International Coalition of Medicines Regulatory Authorities (ICMRA) and WHO released a joint statement promoting the alignment of regulatory agencies on the evidence-based review of vaccines and therapeutics to ensure equitable access to safe, effective, quality-assured medicines for treatment and prevention of COVID-19 worldwide[48]. Other mechanisms to align regulatory authorities around data requirements for COVID-19 vaccines included the COVAX Regulatory Advisory Committee, co-chaired by CEPI and WHO, where 13 regulatory authorities discussed product agnostic development issues[49]. This proved a particularly important forum to ensure that all participating regulatory agencies had input into data requirements taking into consideration their local country situations.

48 WHO, 2020. WHO-ICMRA joint statement on the need for improved global regulatory alignment on COVID-19 medicines and vaccines.
49 The Global Health Network, 2022. Covax: Regulatory Advisory Group.

Optimising deployment of existing innovations – what is already achievable

Analysis of the findings from this exercise indicate that combining the currently available innovations and best practices across vaccine developers could compress development timelines to approximately 250-300 days, approximately a 15-25% improvement over the fastest COVID-19 vaccines. Importantly, this assumes a pandemic where there was experience developing vaccines for a related pathogen on a rapid response platform already in use or under development, and an ongoing requirement for completion of Phase III clinical trials prior to emergency use authorisation (i.e., in a similar context to COVID-19). This also assumes no constraints associated with manufacturing of clinical trial material at an appropriate scale to support development requirements. Figure 3 summarises the estimated timeline compressions that could foreseeably be achieved for each of the major steps in vaccine development.

Significant time-saving could come from optimising the initial stage (preclinical activities) which includes creating, testing, and manufacturing a vaccine candidate that can be used in first-in-human trials (estimated time reduction from 9-14 weeks to 5-7 weeks).

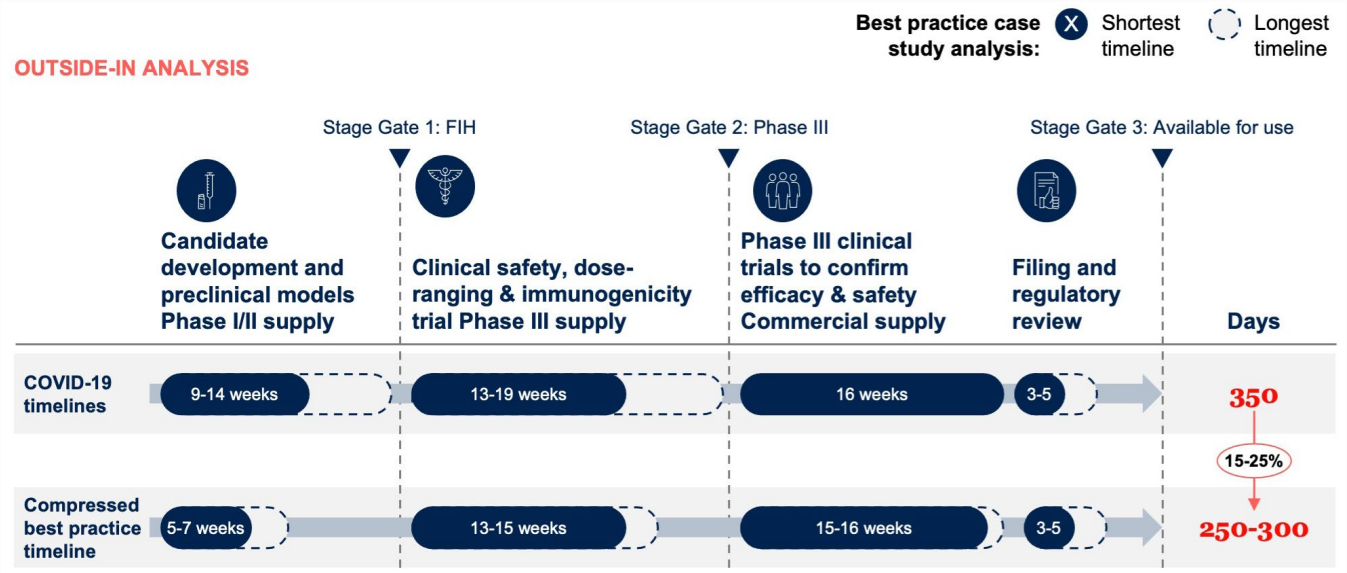
The main opportunity for acceleration during clinical development is combining safety, dosing and immunogenicity testing into a single Phase I/II trial based on knowledge derived from prior development of other vaccines on the platform, instead of conducting two separate clinical trials sequenced over time. This could reduce the time to initiation of Phase III from 13-19 weeks to 13-15 weeks. In addition, shortening the time required to start enrolment in Phase III trials once the interim data of the Phase II trial are available could result in a further reduction of 2-4 weeks.

The duration of the next stage (a large-scale, event-based clinical trial) is highly variable and depends on a variety of factors: (i) enrolment speed; (ii) dosing schedule – this analysis assumes a two-dose schedule given 28 days apart; (iii) epidemiology – which determines the event accumulation rate; (iv) nature of the disease – which determines the time between infection and any illness-related outcome that would serve as a trial endpoint; and v) the length of time required by regulators to accrue sufficient safety data.

The fastest developers have already conducted Phase III trials leveraging most of the innovations discussed above. However, this analysis suggests that further use of best-in-class enrolment methodologies could reduce timelines by 1 week (from the 16-week average), largely by building on predictive analytics and global clinical trial networks to increase the number of trial sites in geographies with high case counts so that events can be accumulated, and the trial endpoint reached faster.

Finally, this analysis indicates that application of the combined best-in-class practices by developers and regulators could accelerate the time for filing and review of the Phase III interim data from the average of 5 weeks to 3 weeks. For example, continuous assessment of data by regulatory authorities could decrease the time between clinical trial completion and authorisation.

Figure 3: Adopting best practices of individual COVID-19 development timelines could theoretically reduce time to vaccine availability to 250-300 days



Further accelerating vaccine development – a paradigm shift

Combining the currently available innovations and best practices across vaccine development into a fully optimised, integrated timeline to achieve vaccine approval by a stringent regulatory authority in approximately 250 days would indeed represent a significant achievement. However, this research and analysis also identified opportunities to accelerate beyond this timeline, including potentially achieving the 100-day aspiration necessitated by the circumstances of future pandemics. This, however, would require a shift beyond the current vaccine development paradigm.

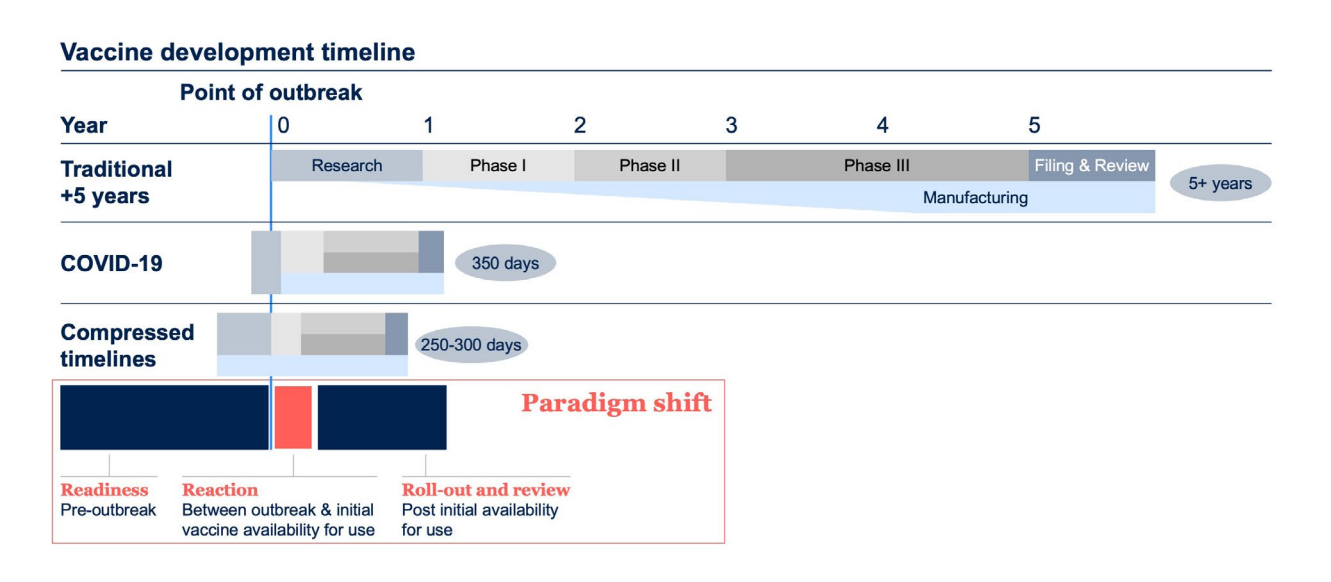
To illustrate the extent of the paradigm shift being contemplated, an analogy can be drawn with the transformation in cycle time of a pit-stop in Formula 1 motor racing. By focusing relentlessly on the core critical path, albeit with a greatly increased level of preparation and parallel processing, what used to take well over a minute can now be done safely in less than two seconds – a reduction of some 97% in elapsed time.

This relentless focus on the clock is critical in an environment where split-second margins are the difference between victory and defeat. To achieve this, Formula 1 teams invested heavily in organisation, process mapping and practice to achieve the minimum possible elapsed time during a pit-stop. However, optimising these incremental gains in and of themselves were not enough. Ultimately the transformation in pit-stop cycle times required a paradigm shift that involved redefining fundamental aspects of Formula 1, including the instrumentation for monitoring race performance, the design of the principal components of the racing car and the types of tools used to maintain and change those components. This required adaptation across multiple disciplines of Formula 1, including technical research and design, development and testing, manufacturing and regulation.

A focus on speed is just as important in vaccine development for pandemic preparedness and response – albeit with far greater significance, given the threat to global health outcomes and economic stability. Nonetheless, a similar set of principles can be consistently applied to reduce cycle time to the minimum possible, and without compromising safety. This research and analysis indicates that optimising incremental gains could shorten the timeline to 250 days but in and of themselves will not be enough to achieve the 100-day aspiration. Ultimately, the transformation in vaccine development timelines will also require a paradigm shift that involves redefinition of fundamental aspects of vaccine development for pandemic preparedness and response. This will require adaptation across multiple disciplines of vaccine development including scientific and technical research, development and testing, manufacturing and regulation.

Figure 4 illustrates how the current vaccine development paradigm for outbreak response could be redefined from one which is described by discrete stages for development, evaluation and intervention to one where many activities are performed in anticipation of a range of threats, and not entirely in response to one in particular. ***At the heart of the new paradigm is a fundamental shift towards preparedness***. This will confer the capacity for rapid reaction to an identified outbreak and provide mechanisms for vaccine roll-out to targeted, high impact groups where there is early positive benefit-risk profile while continuing, in parallel, to amass clinical evidence and larger volumes of vaccine doses for broader roll-out to larger populations. This shift towards preparedness would likely need to be a global effort with appropriate attention in both higher- and lower-income settings.

Figure 4: Achieving the 100-day aspiration will require a paradigm shift for vaccine development



Such a paradigm would come with existing and new operational and clinical risks which would need to be extensively evaluated in advance of a pandemic, and should be pursued only if the right safeguards, particularly regarding safety risks, are put in place. Therefore, the paradigm shift should only be deployed in a future pandemic situation if the scientific progress between now and then has sufficiently advanced to eliminate the most material of these risks and regulatory practices and pathways have been modified accordingly.

This research exercise identified a number of key scientific and technological prerequisites that could underpin this shift: the first prerequisite is the ability to develop a pathogen-specific vaccine during an outbreak by adapting **previously developed and well-characterised prototype vaccines** against closely related viruses; the second prerequisite is the availability and readiness of **global clinical trial infrastructure, standards and tools**; the third prerequisite is the ability to develop and use **more rapid measures of vaccine-induced immune response and protection** thereby shortening the time to determine trial outcomes; the fourth prerequisite is an ability to **rapidly manufacture and validate the first batch of experimental vaccines** that are suitable for human use; the fifth prerequisite is the ability for **early characterisation of the outbreak and pathogen**.

Investment in initiatives to achieve these prerequisites pre-outbreak could provide a level of ***READINESS*** that opens up the ability for ***REACTION* in 100 days**. Under emergency circumstances, vaccine development in response to a new outbreak would then consist of the adaptation of well-understood prototype vaccine candidates into a new pathogen-specific vaccine (circa 5 weeks), immediate testing in a rapidly expanding trial population (circa 8 weeks), and emergency approval for use in the populations with the highest risk profile once the immunogenicity of the pathogen-specific vaccine has been documented but before event-derived efficacy is available (circa 1 week). Evidence generation, including the collection of efficacy data based on the accumulation of events or gathering real world effectiveness data based on an early deployment, would continue after the first emergency use authorisation as part of an ongoing ***ROLL-OUT AND REVIEW***, and be used for staggered approval for use in broader populations and lower risk groups. Potential stages of this new paradigm, together with the key opportunities and challenges associated with achieving it, are discussed in detail below.

Stage I: Readiness

To have vaccines ready for initial authorisation and manufacturing at scale within 100 days of recognition of a pandemic pathogen will require significant investments during the pre-pandemic period to achieve the scientific and technological prerequisites described above. This research exercise identified a number of key innovations, enablers and challenges to achieve each of the prerequisites – the most important of these are discussed below[50].

Prerequisite #1: Pre-existing well-characterised prototype vaccines for representative pathogens across multiple virus families

Creating pre-existing prototype vaccines on select, rapid response platforms will likely allow significant platform-specific experience and knowledge to be built that could then be leveraged for rapid adaptation in the event of an outbreak. Going forward, this would then permit critical activities to be conducted in parallel with human trials, or even be omitted, for example animal toxicology, biodistribution and Development and Reproductive Toxicology studies. This prerequisite requires working on two closely related initiatives: building vaccine libraries and developing rapid-response platforms.

There are fewer than 30 virus families known to cause disease in humans. Initiatives to build **libraries of vaccine constructs against representative pathogens from virus families** presenting the greatest pandemic potential would provide starting points for the rapid creation and testing of vaccine candidates against a new pathogen within a family. Constructs within the library could either be used directly (if sufficient cross-reactivity exists) or adapted rapidly in case of an outbreak. Initiatives to build libraries of prototype vaccines and pan-family constructs would be based on priority pathogen immunogen research and involve identification and selection of antigens to support the development of validated immune assays and diagnostics, and identification of pathogen-specific platform(s) for vaccine development based on immunogen type and optimal immune response.

These initiatives are likely to increasingly utilise **automated vaccine design** – the use of computational models to predict immune responses based on available platform, antigen and pathogen-specific information. Automated vaccine design would enable rapid immunogen identification based on known-structure-activity data from existing (prototypic) vaccines and extrapolation to unknown outbreak pathogens, including prediction of antigen targetability (to avoid vaccine enhanced disease). It is anticipated that, with sufficient pathogen family knowledge and experience, it may be possible to predict platform-related versus antigen-related safety events. This could then enable regulators to further reduce the length of safety follow-up and ultimately utilise a smaller safety database to enable an earlier authorisation in specific sub-sets of the population with particularly favourable benefit-risk profiles, with subsequent longer-term safety and efficacy data enabling broader approval.

50 See Appendix III for the full catalogue of innovations.

In addition, investment in initiatives that further increase availability and understanding of **rapid-response platform** technologies would be required to frontload process development, standardise at scale processes and enable rapid adaptation to new pathogens. There are several platform technologies on which vaccines can be developed, but only a few that offer high ease of modification for new antigens (Figure 5). Moreover, not all platforms are appropriate for different pathogens, therefore it is important to maintain a broad portfolio of platforms. Already today, developers are working on improving mRNA technology, viral vectored and protein vaccines, and advance additional vaccine platforms. Advancement of those platforms, and the eventual licensure of vaccines for existing pathogens on these platforms could provide sufficient experience with the platform to enable almost immediate initiation of human studies in the event of an outbreak of an unknown pathogen. Having a pre-approved **Masterfile of non-variable platform and/or vaccine component safety data** could replace the requirement to resubmit data and enable more streamlined and rapid authorisation during an outbreak. Such pre-optimisation of multiple different platforms for multiple different prototype vaccines – including adaptations to optimise for use in lower-income settings (e.g., thermostability, simplified processes, single dosing schedule, lower cost etc.) – prior to the next pandemic would provide a comprehensive toolkit for global pandemic response.

Further development of these rapid response platforms could enable standard operating procedures (SOPs) to be established for **adapting manufacturing processes** and **pre-defined in-process and release assays** to outbreak pathogens, and using platform data to pre-validate quality control assays. This would require investment in a number of areas, including development of globally standardised assays, including multiplex immunoassays for virus families that can be rapidly adapted to specific novel pathogens, to measure immune response in convalescent sera and vaccine recipients; correlation research to expand use of pseudovirus assays early on to limit reliance on virus availability; building international networks of assay centres with standardised processes, including in lower-income regions, to allow comparability of studies and results across different countries and studies.

With greater platform experience (especially where that experience has been gained developing vaccines for closely related pathogens), and the evolution of regulatory practice, regulators could plausibly approve initial carefully monitored use of a vaccine against an emerging pathogen in much the same way that seasonal influenza vaccines are approved. Leveraging knowledge from SARS-CoV-1 and MERS-CoV to rapidly pivot to SARS-CoV-2 provides an important proof of concept for the speed with which new vaccines can be adapted from existing prototypes. Regulatory guidance issued by EMA, FDA and WHO have enabled rapid adaptation of COVID-19 vaccines to emerging variants and have led to the development of Omicron-specific vaccines by Pfizer-BioNTech and Moderna, which moved into Phase II clinical trials with extraordinary rapidity on the basis of prior platform experience.

Current limitations: There are considerable technical and scientific challenges to overcome in the development of prototypic vaccine libraries, including (but not limited to) the requirement to generate deep structural and genetic knowledge across multiple virus families to optimise candidate and platform development. Given that most of the vaccine constructs developed through prototypic and/or pan-family library approaches would not be evaluated in real life situations in the short-to-mid-term, and advanced analytics and capabilities for use in preclinical vaccine development requires deep (and expensive) expertise, success will be critically dependent upon on the willingness to make at-risk investment of financial resources and time commitments necessary to establish and maintain these libraries to appropriate levels of quality[51]. Since many of these investments are likely to be deployed in development of vaccines to pathogens or diseases that might never emerge as pandemic threats, this would require development of appropriate business models and other incentives in order to attract and motivate commercial developers and talented scientists towards these endeavours. Furthermore, engagement with regulatory authorities will be required to evaluate where platform data can effectively be used to accelerate vaccine development in the context of future outbreaks and for regulatory authorities to review these data in advance of future outbreaks to fully enable development time savings when required.

Figure 5: Further development across multiple platforms is needed to optimise for speed and effectiveness, but not all are likely to enable achievement of the 100-day goal

Timeline suitable for 100 day goal | Potential to reach 100 days (with targeted preparation)

Platform	Description	Minimal time until first batch[1]	Ability to pre-optimise processes prior to outbreak	CD independent of immunogen knowledge	Key limitations	Example vaccines
RNA	Delivery of RNA of antigen using lipid nanoparticles (LNPs)	3+ weeks	✓ Similar process (assuming use of same LNP)		Plasmid DNA can be rate-limiting raw material	COVID-19
Viral vector	Delivery of DNA or RNA of antigen using viral vectors	10-12 weeks	✓ Unique viral banks required	✗ Viral antigen needs to be known & targetable	Long release assays required (e.g., replication competent virus)	COVID-19, Ebola, Zika, influenza, HIV
Recombinant protein	Protein vaccine based on viral antigens	Similar to viral vector	✗ Optimise cell growth, protein folding & formulation w/ adjuvant		Protein folding and formulation difficult to standardise	COVID-19, hepatitis B, shingles HPV
Virus-like Particles	Virus-resembling molecules with multiple surface antigens	Longer than recombinant proteins	✗ Optimise cell growth, protein folding, complex assembly and formulation		Protein folding and formulation difficult to standardise; complex molecules due to need for self-assembly	Hepatitis B, HPV
Inactivated vaccine	Inactivated or altered replication-deficient virus	Speed determined by ability to use high BSL facilities, cell line availability & scalability and viral doubling time	✓ Relatively simple to manufacture but growth may be virus-specific	✓ Whole virus vaccines requires limited knowledge of specific antigens	Weaker immune response / multiple doses; release test to ensure full inactivation	COVID-19, influenza (shot), hepatitis A, polio (shot), rabies
Live attenuated vaccine	Genetically modified virus which does not cause disease		✗ Genetic manipulation unique to virus		Not suitable for people with compromised immune system	MMR, rotavirus, smallpox, shingles, yellow fever

Cell growth required

Timelines until first batch vary between platforms but so does their immune response & side effect profile and need for immunogen identification

1. Excluding release testing
Note: PD = process development; CD = candidate development
Source: External stakeholder interviews, literature research

51 Global pandemic preparedness and response financing requirements are discussed in more detail on pp41-43.

Prerequisite #2: Global clinical trial infrastructure and readiness

Having globally available clinical trials infrastructure in place would facilitate rapid generation of clinical evidence of efficacy and safety by enabling simultaneous testing of multiple vaccines and flexible adjustment of trial sites to include locations with higher disease prevalence. A fit-for-purpose global clinical trials infrastructure would require three different components: a clinical trials network; a clinical laboratory network; and national clinical trial and volunteer registration capacity.

Creating a **global clinical trials network** would entail establishing clinical trials capacity and capability across all continents, including in lower-income settings, which would be routinely active during interpandemic periods, but which could be rapidly leveraged under outbreak conditions. To ensure rapid site activation when needed, all sites across the network would require access to standardised protocols, processes and equipment, trained staff and pre-established trial information management systems for standardised data collection and reporting. Such a global trials network could be achieved through enhancing connection and collaboration between existing regional networks, such as those already established to focus on endemic diseases or localised regional outbreaks. Global networks could also be strengthened through partnerships between global and regional Clinical Research Organisation (CROs) that maintain and utilise clinical trial sites for routine clinical development studies. For example, prior to the COVID-19 pandemic Pfizer had established a strategic partnership with ICON, a global CRO, for the provision of global expertise in planning, execution and management of clinical trials for a number of Pfizer's different therapy areas of interest[52]. This pre-existing relationship enabled the rapid recruitment of over 44,000 participants across 153 sites in the US, South Africa, Latin America and Europe to support global Phase III development of the Pfizer-BioNTech COVID-19 vaccine[53].

An established **global clinical laboratory network** would facilitate faster data readouts in the event of an outbreak by enabling standardised analyses and avoiding the requirement for long-distance shipping of samples. Initiatives to create a global clinical laboratory network would require establishing and sustaining laboratory sites in each continent which would have rapid access to virus samples and adhere to standardised procedures for clinical and biological sample analyses.

Finally prepositioned **national clinical trial and volunteer registries** could serve to accelerate targeted recruitment of high-risk populations during a pandemic. This would require setup of pathogen-agnostic national preregistration for safety and efficacy studies to facilitate rapid enrolment in the event of an outbreak. It would also involve regularly updating national registries so that healthy volunteers can rapidly be contacted, provide consent and be recruited into studies; collecting demographic, lifestyle and co-morbidity information to accelerate recruitment; and implementing novel technology nationally to match volunteers with relevant clinical trials. Some governments have already established national registries, many prompted by the experiences with COVID-19 – for example, the Ministry of Health's Institute of Clinical Research in Malaysia launched a National Healthy Volunteer Research Register (NHRVR) in July 2021 to accelerate vaccine and therapeutics development[54].

52 Pfizer, 2011. Pfizer Announces New Strategic Partnerships With ICON And PAREXEL International Corporation.
53 ICON, 2021. ICON supports Pfizer and BioNTech on the investigational COVID-19 vaccine trial.
54 New StraitsTimes, 2021. NHRVR to help enhance country's capability in clinical trials.

Current limitations: Establishing and maintaining common protocols, standards and systems across multiple facilities globally would require addressing a significant set of political, ethical, logistical, and operational challenges. Furthermore, sustaining the infrastructure during interpandemic periods would require models that generate sufficient routine demand to keep the trial sites and laboratories operational. While partnerships with CROs offer potential opportunities to address a number of these challenges, preparation of plans, contracts and ongoing communication requires significant ongoing investment from all parties involved. Moreover, during an outbreak, competition for trial sites and suitable participants may arise where a CRO has partnerships with multiple developers.

There are several governance risks associated with collecting and managing information compiled by national registries. Personal data and confidentiality legislation, registration hesitance and mistrust towards studies on undefined threats and vaccine technology would all need to be addressed, which would necessitate ongoing investment in a range of efforts to build and maintain public trust.

Prerequisite #3: Earlier biomarkers of robust immune response and protection

Despite the best efforts of vaccine developers, the immune response currently imposes its own timelines to vaccine development. Some reduction in the duration of clinical trials could be achieved by development of earlier biomarkers of a robust immune response and use of *in silico* methods for assessing safety and immunogenicity.

Early markers of protective immune response would help to de-risk and accelerate R&D activities by giving an indication of vaccine efficacy prior to the traditional 14–21-day period taken to observe a full immune response. This would require **identifying immune markers or drivers** from previous vaccine studies to categorise population cohorts, for example by identifying immune non-responders. This would also require immune activity panels to be developed to predict reactogenicity including the level of immune activation, cytokine release and T-cell activation. Use of ***in silico* modelling** for immunogen selection (metagenomics) and correlation with protection levels could offer the ability to understand the potential of an antigen, adjuvant or platform to trigger production of neutralising antibodies or cause specific side effects. *In silico* approaches could also be used to assess potential toxicity based on known structure-activity information of antigens and possible off-targets in the body as well as mechanisms leading to vaccine-enhanced disease. Further development of *in silico* approaches based on more extensive computational modelling of the immune system could also offer the potential to predict vaccine efficacy in the future.

Ultimately, achieving authorisation in 100 days, at least for a sub-set of the population, would likely require a move away from event or outcome-based efficacy data to scientifically sound, pre-agreed use of validated, early immune response markers of efficacy. This would require amassing sufficient platform and pathogen knowledge to identify, validate and gain acceptance of new biomarkers, and then developing and validating rapid adaption protocols for clinical and CMC assays (e.g., immune response, product characterisation and release, process control and diagnostic assays) prior to an outbreak.

Use of early biomarkers of immune response could only be leveraged realistically in sufficiently grievous situations – for example, very high case fatality and transmissibility rates – with favourable benefit-risk profiles for doing so. In such cases, authorisation would likely be limited, and vaccine use would not obviate the need for large-scale Phase II/III trials in broad, representative populations to obtain clinical efficacy and longer-term safety data in parallel to the initial limited use. There is some precedent for use of immunogenicity endpoints for a new vaccine: the FDA provided fast-track designation to a Chikungunya vaccine based on a pre-approved immunogenicity endpoint[55,56]. Also, some countries used immunogenicity data for early approvals of COVID-19 vaccines (e.g., Russia, India and China) without causing evident harm, although none of the stringent regulators followed that path[57]. Russian and Chinese regulators, which released vaccines for emergency use as early as July 2020, imposed a post-EUA requirement for Phase III clinical trials to document efficacy.

Current limitations: The power of artificial intelligence and machine learning for *in silico* modelling is being widely explored, however it has yet to be fully translated into clinical development. While the computational technology is relatively mature, its application is limited by the extent of current biological and immunological understanding. More fundamentally, current gaps in our understanding of biology and immunology present limitations for the identification and validation of early biomarkers to predict immunogenicity and vaccine efficacy.

Progress in these areas will therefore necessitate further scientific advancements and new discoveries. For example, there is currently limited ability to extrapolate between different variants or viruses in the same family due to complex biology – as seen in the differing ability of different SARS-CoV-2 variants to escape the immune response. Further research to identify early immune markers reasonably likely to predict efficacy across different viruses in the same family would be necessary in order to rapidly inform or predict vaccine efficacy in the event of an outbreak of a novel pathogen within the family. Additional considerations will exist for multi-dose vaccines, where early markers (i.e., after the first dose) may be less informative of overall immunogenicity and vaccine efficacy.

55 Valneva, 2018. Valneva Awarded FDA Fast Track Designation for Chikungunya Vaccine Candidate.

56 FDA, 2019. FDA Briefing Document: Vaccines and Related Biological Products Advisory Committee Meeting.

57 Kyriakidis, et al., 2021. SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. npj Vaccines 6,28.

Prerequisite #4: Global capacity for rapid manufacture and validation of experimental vaccines

The ability to rapidly manufacture and validate the first batch of experimental vaccines that are suitable for human use is critical to achieving the 100-day aspiration. The timeline for doing this is platform-dependent, but these activities should be achievable within 5 weeks for mRNA vaccines. Optimising manufacturing processes for rapid initial production and subsequent scaling, having commercial-quality raw materials ready, and developing clear procedures and checklists for rapidly adapting existing processes to a new pathogen can all be accomplished in advance of an outbreak.

To achieve this for a range of different rapid response platforms would require global deployment of a suite of engineering innovations to enable greater standardisation and incremental time savings. This would include initiatives to **standardise manufacturing facilities and systems** through global use of standardised, interchangeable parts to reduce complexity of supply chains, and adoption of 'plug-and play' Quality Management Systems (QMS) for rapid technology transfers between manufacturing sites. Global standardisation could be incentivised by making financing for new facilities dependent on their adoption of agreed global standards, including for release assays. It would also include initiatives to promote the **use of continuous manufacturing suites** which reduce footprint and cost of facilities and increase overall productivity, resulting in more affordable vaccines. Continuous manufacturing suites are also more readily maintained as 'warm' facilities during interpandemic periods. In addition, initiatives focused on broader adoption of novel **manufacturing innovations** could further optimise fill and finish processes – for example the use of special vial coatings that enable faster movement of vials through machines without breakage, or more widespread use of multi-dose bags to increase capacity and reduce overall resource utilisation.

While manufacturing optimisation is critical for speed, especially within the first 100 days, scale of production is equally important for the longer-term response. Readiness to ensure scaling capacity could be achieved by maintaining a **global network of 'warm' manufacturing facilities and reserved capacity for multiple different platforms** which could be activated within days or weeks to produce vaccines in response to an outbreak. This would require funding the creation and maintenance of a global network of facilities that provide coverage across multiple different platforms including mRNAs, viral vectored and protein vaccines, ensuring not only readiness of capacity but also, critically, of skilled and experienced talent and capabilities. This may also require incentives and agreements to facilitate rapid technology transfer protocols with simplified processes, pre-prepared dossiers and effective partnerships with contract development and manufacturing organisations (CDMOs).

Broad geographic diversity would be a critical success factor for the global network and would require significant investment in establishing new manufacturing facilities in lower-income regions, traditionally devoid of vaccine manufacturing capability. Moderna has recently signed a memorandum of understanding with the Government of the Republic of Kenya to build state-of-the art mRNA facility in the country with the goal of producing up to 500 million doses of vaccines each year[58]. Other similar initiatives are underway, especially on the African continent, which until 2021 imported 99% of its vaccines[59].

Additional initiatives that would improve the robustness of global supply chains would be necessary. These include enhanced modelling and forecasting, removal of import/export controls, and expansion of capacity for manufacturing and stockpiling (including cold chain capabilities for distribution).

58 Moderna, 2022. Moderna Announces Memorandum of Understanding with the Government of the Republic of Kenya to Establish its First MRNA Manufacturing Facility in Africa.

59 Nature, 2022. Africa is bringing vaccine manufacturing home.

Current limitations: Establishing new manufacturing sites, transferring technology and contracting with CDMOs is complex, time-consuming and costly, and requires engagement across a broad range of different stakeholders. This is an area where public-private partnerships should be encouraged. However at the global level these challenges are further heightened by political, legal and logistical hurdles that will need to be overcome. For example, new policy mechanisms are required to enable effective management of intellectual property (IP) during an outbreak to reduce barriers for short-term local and regional production of vaccines, particularly in lower-income settings, while ensuring commercial developers retain appropriate incentives for long-term investment in innovative vaccines. Political and logistical hurdles affecting supply chain readiness are also likely to manifest in situations where there is increasing demand for consumables, for instance during an outbreak, when national interests are most likely to prevail.

Prerequisite #5: Global capabilities for early characterisation of pathogens and outbreaks

Early characterisation of a pathogen and outbreak is critical for rapid initiation of vaccine development, both to identify the types of individuals at highest risk of becoming infected so that trial enrolment strategies can be developed, and to inform benefit-risk estimates on which regulatory decisions can be based. Outbreak surveillance and disease epidemiology capabilities need to have global coverage to ensure that an early alert trigger can be raised wherever in the world an outbreak occurs.

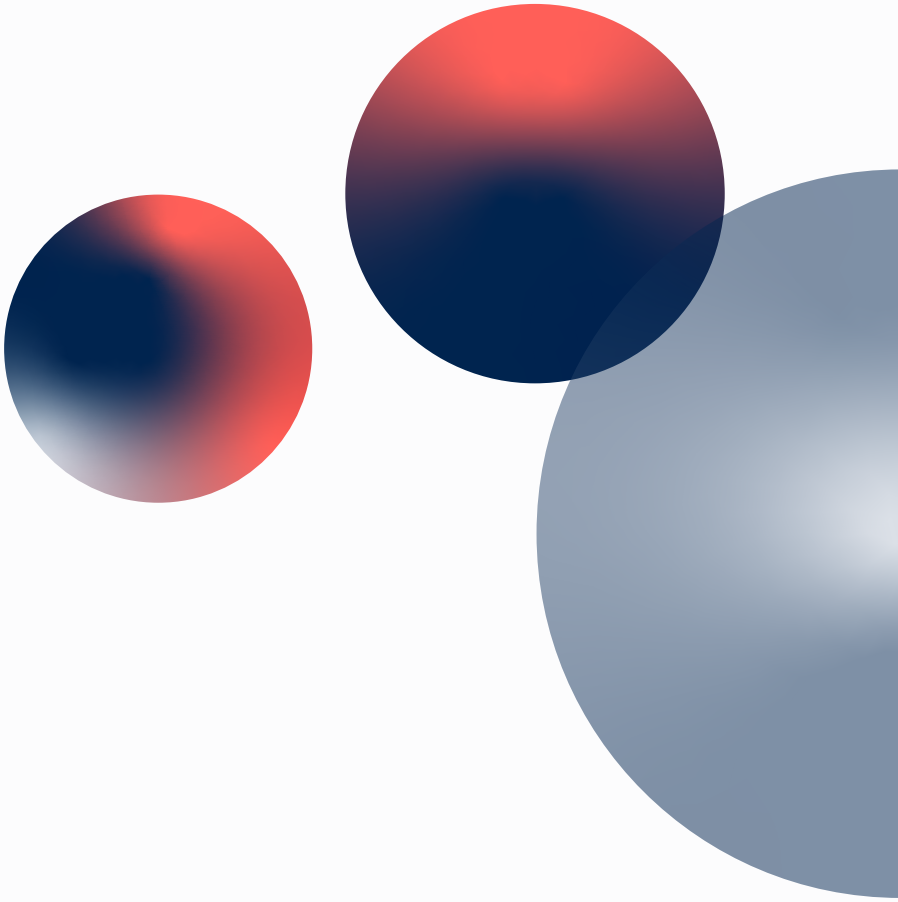
Active, continuous global surveillance of infections and localisation of infectious incidence to enable faster alert triggers could be achieved by building on local epidemiological networks and partnerships in regions that monitor viral strains and zoonosis events. Strengthening the capabilities of regional centres could lead to both: i) improved scientific understanding, for example through the use of continuous mutational analysis of virus species known to infect humans as well as viruses from spill over events; and ii) better tracking of the spread of pathogens in real-time using data verified by 'on the ground' contributors – for example, through specialised platforms enabling individuals to report cases via mobile technology. Surveillance networks would ideally all adopt a set of **global agreements on sequence sharing**, standardised sequencing protocols and real-time repository systems that uphold the independence of national governments while promoting trust and reliability in surveillance reports.

Existing surveillance capabilities played a critical role in monitoring the evolution of the COVID-19 pandemic. For example, scientists at the Botswana-Harvard AIDS Institute Partnership identified the Omicron variant in four international travellers to Botswana, rapidly notifying the WHO and thereby enabling countries and regional organisations to react rapidly to the spread of the Omicron variant – including the rapid initiation of vaccine adaptation efforts[60].

Establishing a global surveillance network would provide a mechanism for raising alert triggers to initiate global vaccine development efforts and to guide the scale of response efforts by rapidly simulating disease parameters through advanced data processing tools. This would require international alignment on the **criteria for triggering a global alert**, including agreement on pre-defined thresholds and categories of alert. It would also require the development of novel collaborative approaches to rapidly investigate disease characteristics including common **data collection systems** that enable datasets from multiple sources to be made available via a single point of access; shared **simulation, analytical and processing tools**; and enhanced **knowledge and information sharing platforms**.

60 WHO, 2022. Botswana, South Africa deepen probe into new Omicron sub-variants.

Current limitations: A successful global network for early characterisation of pathogens and outbreaks would require highly localised expertise, processes and infrastructure to be established in regions where investments in surveillance are not prioritised. Additionally, measuring pathogen transmission, especially for those with zoonotic potential, requires human-to-human, animal-to-human and animal-to-animal monitoring – expertise that is not always readily available. Efficient global surveillance requires effective national, regional and global interdisciplinary collaboration[61], and political and logistical challenges to be overcome. For example, it would be critical to ensure alert response is elevated above national interests to avoid situations where nations fail to raise an alert due to fear of restrictive measures being imposed, such as unilateral border closures. Effective disease characterisation modelling would also require strengthening the capacity for interdisciplinary collaboration between 'on-the-ground' bioinformaticians, researchers, statisticians, epidemiologists, data scientists and developers to gather real-time information on infections and outbreaks. Data use policies and referencing guidelines will also need to be established to help individual developers protect IP rights by controlling access and use of data, and monitoring compliance. Importantly, regulatory authorities must be engaged in global surveillance and characterisation efforts to ensure operational processes and practices are established based on appropriate guidance.



61 WHO, 2022. Strengthening the Global Architecture for Health Emergency Preparedness, Response and Resilience: White Paper for Consultation, Geneva: WHO.

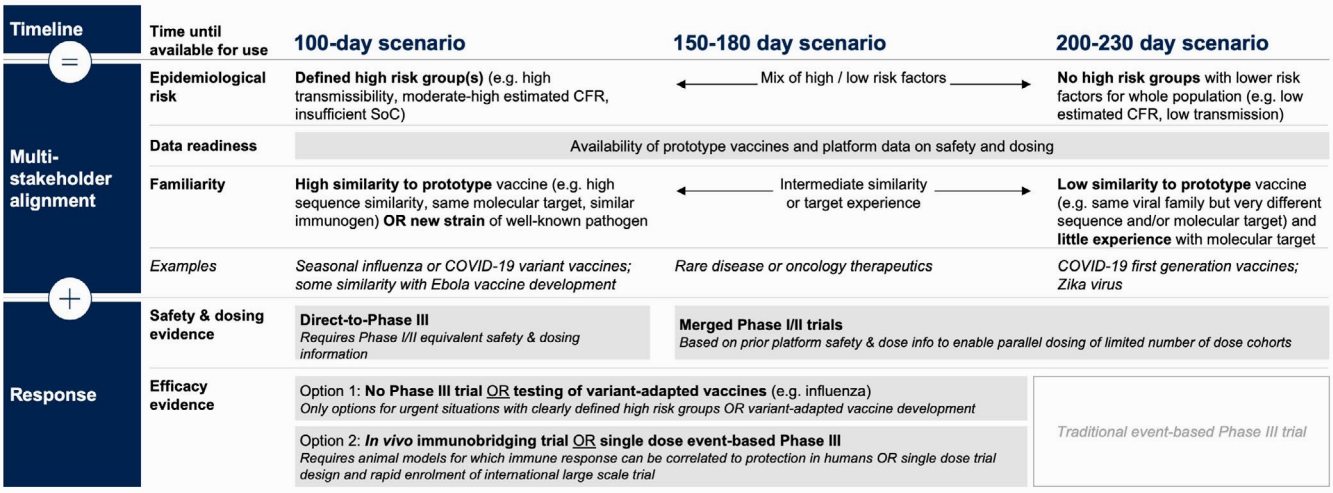
Stage II: Reaction

Investment in initiatives to achieve the prerequisites described above during the pre-outbreak *READINESS* stage would provide the opportunity for rapid reaction in the event of an outbreak. While the aspiration is to be able to react within 100 days of recognition of a pandemic pathogen, not all situations will require vaccines to be developed in 100 days. Emergency vaccine development is, by definition, higher risk than development in interpandemic periods. That said, it is important to ensure that unnecessary risks are not taken, and it is critical to remain scientifically grounded throughout the vaccine development process, particularly with regard to safety and efficacy.

Even with maximum preparedness, the length of any given scenario-specific reaction period will vary (Figure 6) and will depend on several factors, including understanding of the safety and efficacy profile of the vaccine candidates at that time, and the severity of the situation (e.g., virulence, morbidity, and mortality of the pathogen). This, in turn, will dictate the anticipated benefit-risk profile in the general population versus in specific populations at risk for severe disease. Similarly, the feasibility of developing a vaccine will depend on factors such as the availability of data from prior research on a comparable prototype vaccine, familiarity with the pathogen or its viral family, availability of sufficient financing, and the level of collaboration between partners.

In practice, this research and analysis supports the proposition that vaccines could be available for use within 100 days to more than 300 days from recognition of a pandemic pathogen. However, in the early stages of a potentially serious outbreak where limited data on pathogen characteristics or epidemiology is available, waiting for the full picture to emerge could mean wasting valuable time. In such cases the aim of making vaccines available within 100 days should be the 'default' goal, which would be continuously re-assessed as new data emerges. The following section describes in more detail what a 100-day reaction pathway could look like and discusses specific scenarios in which this may or may not be achieved[62].

Figure 6: Factors influencing the speed of vaccine development in response to an outbreak



62 See Appendix IV for a case study describing the different paths for vaccine development once an outbreak is declared.

Reacting to an outbreak in 100 days

Once an outbreak has been identified, the reaction pathway would proceed in three phases: ***i) immediate response*** to develop and manufacture pathogen-specific vaccines through adaptation of well-understood prototype vaccine candidates (circa *30 days*); ***ii) evidence generation*** through immediate testing in a rapidly expanding trial population (circa *60 days*); and ***iii) filing*** for emergency approval for use in populations with the highest risk profiles once the immunogenicity of the pathogen-specific vaccine has been documented, but before event-derived efficacy is available (circa *10 days*). During this period, it is critical that appropriate approaches for outbreak response through non-pharmaceutical interventions, and where available therapeutic interventions, are deployed to control the outbreak until vaccines become available.

i) Immediate response (circa 30 days)

In response to alert trigger, vaccine developers would immediately initiate vaccine development, designing the pathogen-specific candidate based upon existing knowledge of prototype vaccines developed for the same virus family and rapid response platforms. In a situation where a prototype vaccine candidate already exists for the pathogen, design of the new vaccine could conceivably be achieved within 2 days. In parallel, development of immunoassays, including multiplex immunoassays, would be initiated through international networks of assay centres and global serum collection networks. Under ideal conditions, this could be achieved in 5 weeks. In parallel, manufacturing of initial and large-scale clinical batches would be initiated based on prior manufacturing experience of the platform. With sufficient prior experience of the platform, this could be achieved in 5-7 weeks.

Meanwhile, information relating to the outbreak and pathogen would continually evolve, especially during the early stages of an outbreak. Early and ongoing pathogen and outbreak characterisation efforts through coordinated activities of key stakeholders from affected countries, developers, regulators, policymakers, normative bodies, institutions and funders would include: confirmation of transmission mode and rate; estimation of case fatality rate (CFR) and determination of high-risk groups based on initial cases; clarification of scale and location of initial outbreak and risk of potential global spread; mapping of available healthcare infrastructure (e.g., clinical trial networks) to understand gaps and ensure accelerated response; determination of benefit-risk assessment and alignment on appropriate development paths; provision of regulatory guidance on non-vaccine development efforts (e.g., assay development).

A number of innovations and approaches identified from the research exercise could enable development and manufacture of initial clinical batches of pathogen-specific vaccine candidates within 30 days.

The time to first-in-human trials could be significantly accelerated by **taking preclinical studies off the critical path** and conducting first-in-human studies in parallel with studies on toxicology and tissue distribution. This could be achieved by using pre-existing supporting evidence generated through prototypic vaccine research and development and prior use of the rapid response platform. Meanwhile assay optimisation bottlenecks could be minimised by rapid adaptation of pre-existing multiplex assays developed for virus families to the specific novel pathogen, using validated adaptation protocols.

Initiating at risk clinical and commercial scale manufacturing for initial clinical batches and in preparation for roll-out post-authorisation would require activating CDMO contracts and manufacturing units globally in preparation for equitable deployment. This would require GMP readiness and technology transfer activities to commence immediately after candidate selection, including development of appropriate release assays. Conducting these manufacturing steps in parallel could save approximately 2 months in the overall vaccine development process. In addition, mass vaccine production could be accelerated by expanding emergency manufacturing capacity through rapid technology transfer to 'warm' facilities. This would require activation of pre-developed operational plans for pandemic vaccine response and would involve rapid repurposing of active manufacturing facilities according to pre-agreed terms and conditions. This could cut 1-2 weeks off the overall timeline.

To ensure global accessibility, decentralised modular units for manufacturing and clinical trials could be deployed. To minimise deployment time, especially in countries and regions with limited manufacturing or clinical trial infrastructure, these units could be stationed in difficult to reach and underrepresented locations during interpandemic periods. For example, mRNA printers are portable automated production units for mRNA vaccines, made possible by the relatively simple biochemical process for production of RNA molecules. These printers are capable of producing over 100,000 vaccine doses over the course of a few weeks and could therefore be rapidly shipped to remote locations to serve the local and regional populations. They would also allow for rapid optimisation of mRNA vaccine candidates, for example in the event of a strain change or to improve properties such as thermostability or potency. It is important to note that for decentralised deployment in support of development and production of a specific vaccine product, these modular units would need to operate with standardised clinical trial protocols to enable pooling of clinical data, and/or as part of a scaled manufacturing process to ensure consistency of product.

Vaccine development pathways and decision points may require frequent readjustment as more and more accurate information relating to the outbreak and pathogen emerges. **Pre-programmed CFR and benefit-risk models** using computational algorithms that reliably extrapolate case fatality rates based on multiple parameters could be used to support rapid determination and adjustment of benefit-risk profiles for specific populations and associated vaccine development pathways and decision points.

Several challenges could impact the ability to develop and manufacture initial clinical batches of pathogen-specific vaccine candidates within 30 days. Rapid antigen identification is not always possible, especially for virus families where the host target is unclear. Indeed, there is a likelihood that not all future pandemic-causing pathogens will be readily targeted by vaccines, as evidenced by experiences to date with HIV. In addition, reliable serum is not always accessible to enable fast and high-quality assay development. When it comes to manufacturing, speed will depend upon the platform of choice[63]; the ability to activate 'warm' facilities and conduct rapid technology transfer of pathogen-specific processes; and the ability to source raw materials and consumables from existing stockpiles or pandemic supply chains and conduct additional process development to optimise output for the outbreak pathogen. Finally, although computational models were used to build benefit-risk models during the COVID-19 pandemic, it is important to acknowledge their reliance on complex assumptions for modelling CFR, which can significantly affect the reliability of their output.

63 See Figure 5

ii) Evidence generation (circa 60 days)

Once the first clinical batches have been manufactured, vaccine developers would build upon existing clinical evidence on safety and dosing from previously generated prototype vaccines and rapid response platforms to select one or two doses for clinical testing in an expanding trial population. In parallel, non-clinical studies would be conducted to compare the immune response and levels of protection observed in animal models with data in humans.

The clinical trial design would depend upon the outbreak scenario. An event-driven study could be feasible in a pandemic situation if there is a sufficiently large available trial population, whereas a clinical immunobridging study could be used if there is sufficient evidence of correlation between nonhuman and human immune responses. Where a prototype vaccine already exists for the outbreak pathogen, testing of variant-adapted vaccines using pre-established animal models and small human trials may be sufficient, as evidenced for COVID-19. In some circumstances, for example where available clinical evidence indicates high potential benefit for high-risk groups, additional studies to support emergency authorisation may not be deemed necessary, in much the same way that seasonal influenza vaccines are approved currently. Any of these approaches could yield results in as little as 8 weeks for a single-dose vaccine, including interim safety assessments, if the conditions are favourable and operations management is highly proficient.

A number of innovations and approaches identified from the research exercise could enable evidence generation within 60 days.

Having a **single-dose efficacious vaccine** could significantly accelerate vaccine development by obviating the need for a time interval between doses. Alternatively, the ability to extrapolate an immune response after the first dose of a multi-dose vaccine to subsequent doses in the regime based on **early biomarkers of robust immune response** could confer a similar degree of acceleration. However, single-dose vaccines also offer additional advantages for manufacturing and distribution, especially in remote regions with limited healthcare infrastructure.

Depending upon the outbreak scenario, a range of study designs could be adopted for clinical testing of pathogen-specific vaccine candidates. Given the high degree of risk associated with emergency vaccine development, in many cases it would be important to facilitate the simultaneous evaluation of multiple different candidates targeting a range of different immunogens across a variety of rapid response platforms, whilst also anticipating a significant level of attrition due to candidate failure or active down-selection. The ability to conduct **rapid efficacy assessments for multiple vaccines and dosing regimens through innovative trial designs including merged, adaptive and platform trials** would permit rapid comparison across vaccine candidates whilst also reducing the need for large placebo groups. Furthermore, an early focus on identifying and testing vaccine candidates in high-risk populations, including in lower-income settings, combined with tailoring evidence requirements according to outbreak- and population-specific benefit-risk profiles would enable the use of limited efficacy data to support rapid initial roll-out.

Depending on available nonhuman and human evidence, **clinical immunobridging studies** could be used to accelerate development timelines by generating evidence of efficacy for a novel vaccine candidate based on a robust relationship between the protective immune response seen in animals and clinical immunogenicity (or 'predictors of efficacy') between nonhuman and human immune responses, in place of a clinical vaccine efficacy trial. Furthermore, depending on the benefit-risk profile of the vaccine candidate and the outbreak, **controlled human infection model (CHIM) studies** could also potentially be used to accelerate generation of evidence of safety and efficacy, as well as providing opportunities for pathogen and outbreak characterisation. However the time taken for development of appropriate and relevant human challenge models would need to be significantly reduced for these models to meaningfully accelerate evidence generation.

As well as deployment of digital technologies for real-time data collection and monitoring to accelerate execution of clinical trials, innovative digital approaches could also be used to support rapid evidence generation, particularly in cases where there is low availability of subjects for clinical trials. For example, the use of **digital twins**, i.e., comprehensive, longitudinal, clinical records created using baseline data collected from a subject before they receive their first dose, could potentially be used to support safety and efficacy trials by evaluating vaccine candidates using virtual control arms in place of volunteers, or by modelling the effects of behavioural adaptation.

Several challenges could threaten the ability to generate sufficient safety and efficacy evidence to support emergency authorisation within 60 days. There is evidence to indicate that immune responses to some single-dose vaccines decrease sharply over time, therefore, more research is needed to understand the circumstances under which single-dose vaccines are likely to be effective enough, if used early enough, to prevent or stop a pandemic.

Deployment of innovative clinical trial designs may also present numerous challenges. For example, merged clinical trial designs may be perceived as higher risk by some developers due to removal of interim checkpoints where development would usually be paused if certain criteria were not met. Adaptive trial designs may present a number of challenges including recruitment of sufficient eligible subjects when adaptations occur; risk of selection bias owing to adaptations within pre-defined cohorts; and likelihood of delays arising from the need for more complex regulatory guidance and ethics committee approvals for design and planning of adaptive trials. Platform trials may also face challenges in securing participation of commercial developers due to the risk that direct comparison of their vaccine candidate with those of their competitors may negatively impact the commercial value proposition for their potential future product portfolio. Meanwhile, use of immunobridging studies is often restricted by a lack of robust biomarkers of immune response and the limited applicability of correlates of protection from patients that have recovered from infection or from animal models to inform vaccine development.

In addition, the use of CHIM studies presents several challenges and the time taken for development of appropriate and relevant human challenge models would need to be significantly reduced for these models to meaningfully accelerate evidence generation. More importantly CHIM studies may be associated with a non-negligible risk to human life and wellbeing when a disease caused by a novel pathogen is poorly understood, for example the risk of harm from under-attenuated challenge in a situation where rescue medication is unlikely to be available. The use of these approaches would therefore require transparency in communicating risks to potential study participants and in building and maintaining public confidence in scientific methods and vaccine intervention. Finally, the use of digital twins for clinical development is a new area that will require significant work to establish regulatory acceptance of data generated through these approaches, while the replication of biomarkers of a real human through these approaches also raises complex ethical questions that remain to be addressed.

iii) Filing (circa 10 days)

Once sufficient evidence of safety and immunogenicity has been generated and assembled, regulatory authorities would make a final decision whether to grant authorisation for initial use in populations with the highest risk profiles. This decision would be based on ongoing rolling reviews of clinical evidence by the regulatory authorities enabled by real-time data sharing, and this final review of remaining critical path information including product labelling and determination of commitments for further data provision by the developer, could be completed within a week provided appropriate infrastructure and resourcing levels were in place. In parallel, data from the first commercial batches would be reviewed and ready for release at the point at which emergency approval is granted.

A number of innovations and approaches identified from this research exercise could enable rapid regulatory review and authorisation. Effective deployment of these approaches during an outbreak would be contingent upon pre-establishment and/or modification of regulatory practices and pathways during the pre-outbreak READINESS stage of the new development paradigm, and if fully optimised, could accelerate the timeline of the REACTION stage by approximately 1 month.

Initial authorisation of vaccine within 100 days of a new outbreak would utilise an appropriate **pre-defined benefit-risk emergency authorisation pathway** based on the nature of the outbreak and the pathogen. This would be based on regulatory authorities having established a set of emergency authorisation pathways and requirements under different benefit-risk scenarios with pre-defined acceptable trial designs and endpoints to enable rapid initial authorisation in high-risk populations. **Accelerated authorisation pathways** based on interim data and a smaller number of accrued cases could be possible in certain situations, provided sufficient safety data was available, for example a pre-approved **Masterfile of non-variable platform and/or vaccine component safety data**. In addition, mechanisms that permit **vaccine roll-out in consenting populations** on the basis of sufficient safety data could be used to accelerate vaccine availability for use in consenting target populations while controlled efficacy studies continue and other real word data gathering studies are initiated to confirm effectiveness and enable subsequent broader deployment.

Rapid regulatory review and authorisation would be based on **continuous developer-regulator communication**, leveraging effective relationships with both regulatory agencies in affected countries and with stringent regulatory authorities, and using digital tools and technology to enable real-time data sharing and review and optimised feedback cycles. Rapid global response would also be enabled by **aligned requirements between regulatory authorities** and the availability of pre-approved clinical trial designs and clinical trial protocol templates that could be rapidly adapted by developers. This would be made possible by harmonised definitions of data requirements across different regulatory authorities, and agreements in place with developers to enable information sharing between regulators.

Several challenges exist to achieving such rapid regulatory review and authorisation of emergency vaccines. There are numerous potential pandemic scenarios and while pre-defined benefit-risk emergency authorisation pathways could be established for a number of these, it will not be feasible to address every possible scenario. Furthermore, benefit-risk determinations may differ from country to country, presenting challenges for alignment on ethical frameworks and parameters and evidence requirements for authorisation. In addition, accelerated authorisation pathways will require significant investment in building and maintaining public trust to mitigate risks of vaccine hesitancy, which could arise on the basis of potential safety concerns or in the event of failure to meet efficacy expectations following initial authorisation or roll-out in consenting populations. Finally, it is important to note that very few, if any, regulatory agencies are likely to have the resources to engage long-term and on an ongoing basis with multiple different developers and with other authorities across different geographies, which places limitations on the speed of regulatory review and authorisation, particularly for situations initially viewed as low urgency.

Stage III: Roll-out and review

Vaccines receiving initial emergency use authorisation would be rolled out to specific populations for which regulatory authorities had determined a positive benefit-risk profile based on initial clinical evidence, including platform safety data. In parallel to initial roll-out, evidence would continue to be accumulated through ongoing clinical trials and initiation of new studies to support staggered approval for use in broader populations and lower risk groups over time. At this stage manufacturing and production capacity would likely be the rate-limiting factor for meeting initial, potentially rapidly growing, demand. As the number of vaccinated individuals increased, the **collection of real-world observational effectiveness data** through different mechanisms, including prepositioned national clinical trial and volunteer registries, would enable vaccine performance to be monitored in the context of the evolution of the outbreak and longer-term safety and effectiveness questions to be addressed.

Ongoing assessment of effectiveness and safety after initial authorisation would provide the detailed evidence necessary to inform and enhance future vaccine use (e.g., extending use to lower-risk groups and optimising dosing intervals for multi-dose regimens). This would enable key stakeholders including vaccine developers, regulatory authorities, governments, international institutions and policy makers to work together to define the pathways towards full approval. Critical innovations and approaches identified from the research exercise could enable effective parallel vaccine roll-out-and review.

In order to grant initial emergency authorisation, regulatory authorities would require assurances that comprehensive post-authorisation evidence generation activities to support full approval will be conducted. The use of pre-defined standards for post-authorisation studies with clear upfront guidance on requirements for post-authorisation safety (PASS) and effectiveness (PAES) studies that are linked to harmonised trial designs, would help developers and regulators ensure both efficient and robust trial setup during an outbreak. The need for harmonisation is particularly important for PASS which are typically highly variable in design and quality due to utilisation of non-standardised methodologies. For commercial developers this would require aligning and satisfying both marketing objectives and scientific goals and ensuring appropriate resource allocation, which may present challenges for developers seeking to maximise the commercial value proposition for a potential future product. Moreover, because most post-authorisation surveillance studies have traditionally been conducted in higher-income countries (where innovative vaccines have usually received first approval), there remains a significant gap in capabilities and infrastructure for post-authorisation evidence generation in lower-income regions.

Following initial stringent regulatory approval, the WHO EUL process, fully deployed during the COVID-19 pandemic, has proven to be particularly successful as a recognition and reliance procedure enabling vaccine deployment in many countries worldwide. Review of emergency legislation or the need for emergency legislation in countries that were unable to accept WHO EUL could enable even broader country deployment. Emergency legislation could also be evaluated and adapted to ensure that other recognition and reliance procedures can be deployed in the event that an outbreak is more regional and where a WHO EUL process may not be activated.

Rapid vaccine roll-out would likely necessitate the use of **rolling shelf-life reviews** whereby initial authorisation would be granted without extensive stability data, which would subsequently be generated in parallel with initial roll-out. Manufacturers would be required to specify 'date of manufacture' rather than 'expiry date' while shelf-life review takes place. Rolling shelf-life reviews would rely on previous knowledge of expected shelf-life gained from previous use of the platform and for prototype vaccines, while accurate tracking of batches would be necessary to ensure that updates or recalls based on new data relating to effect of changes in geography, storage or climatic conditions on product stability – and consequently shelf-life – could be implemented. Use of barcodes for labelling would enable shelf-life data to be updated electronically without consequences for existing labelling and packaging. Rolling shelf-live reviews would also require clear communication with the general public and end-users on the benefits and potential risks, so as not to undermine vaccine confidence.

Finally, continued use of the **rolling review process** beyond initial authorisation would enable accelerated review of new data towards full approval. This would require upfront investments in infrastructure, digitalisation and process development, especially in lower-income countries. It would also require ongoing commitments from developers to release information which may be commercially sensitive, along with continued additional resourcing by regulatory agencies that are also likely to be dealing with routine and outbreak-related submission backlogs.

Beyond the first 100 days

This research exercise focuses on the scientific and technological innovations in vaccine development required to achieve speed in responding to an outbreak. Of course, what happens once vaccines are developed is critically important to achieving the ultimate goal of stopping or preventing a pandemic. Readiness to manufacture vaccines at scale around the world, and plans for their procurement, distribution, and administration down to the last mile, are critical. For that to happen as quickly as possible, many preparatory activities will need to start in the first 100 days concomitant with vaccine development and testing. Prerequisites for this include the availability of prepositioned funding for vaccine procurement on day one of a potential pandemic outbreak and strengthened global manufacturing capacity and in-country deployment capabilities.

A paper[64] by the Center for Global Development (CGD) notes the existing landscape of medical countermeasures (MCM) manufacturing capabilities and draws lessons from the COVID-19 current pandemic response to suggest eight areas for action along with near-term recommendations to the global community to both prepare and respond to future pandemic risks. The recommendations made in the CGD report include developing a vision and roadmap to slow or stop pathogen spread by: **(1) deploying MCM quickly** (i.e., within 100-200 days from identification of a pandemic threat); (2) ensuring **better visibility of manufacturing capacity** and needs; (3) creating an **Advance Commitment Facility** that releases day-zero financing to jumpstart R&D and global and regional MCM manufacturing; (4) assuring **R&D investments facilitate global access and distributed manufacturing**; (5) devising strategies to **sustain MCM demand during inter-pandemic periods**, with benefits for the fight against current infectious diseases; (6) expanding **regulatory capacity and harmonisation**; (7) establishing a 'mission control' approach for **global and regional governance and coordination**; and (8) supporting **policy research to assess uncertainties and test innovations for ongoing MCM initiatives.**

The 'second 100 days mission' advocated in the CGD report builds on the 100-day aspiration towards a coordinated strategy to ensure speed, equitable and at scale manufacturing and procurement of medical countermeasures to address pandemic risk.

64 Glassman, A., Guzman, J., Kaufman, J. & Yadav, P., 2022. Rapid and Equitable Access to Medical Countermeasures: Lessons, Landscape, and Near-Term Recommendations, Washington, DC: Center for Global Development.

An enabling policy and financing context

Many of the challenges to implementing the scientific and technological innovations identified from this research relate to the policy and financing architecture for epidemic and pandemic preparedness and response. A number of areas relating specifically to regulatory policy have already been discussed in the context of the relevant scientific and technological innovations, including examples of regulatory collaboration and pragmatism during the COVID-19 pandemic which enabled preclinical and human trials to be conducted simultaneously based on previous data generated from within the same technology platform, clear articulation of criteria for safety and efficacy, the employment of non-traditional trial designs, and rolling review of regulatory dossiers. In preparation for the next pandemic, further innovations could include relatively straightforward changes such as a detailed globally harmonised template for regulatory dossiers, potentially based on improvements to the existing Common Technical Document, and advanced benefit-risk assessment methodologies to provide additional guidance regarding the data needed to support emergency authorisation or approval. Other innovations that would help – such as the assessment of the role *in silico* modelling can play in the analysis of benefit and risk, the creation of robust criteria and approaches to authorise vaccine use on the basis of immunogenicity data, and the agreement on the circumstances under which this is warranted – present harder challenges.

More generally the global response to COVID-19 exposed the fragmented and uncoordinated nature of the current global preparedness and response architecture for emerging infectious diseases of outbreak, epidemic and pandemic potential. Lack of coordination and clarity of roles; absence of established surge financing mechanisms for R&D and at-risk manufacturing and procurement; and lack of mechanisms to enable global access to vaccines, diagnostics, therapeutics and critical equipment, has resulted in significant delays in vaccine manufacturing and highly inequitable access to vaccines. An accelerated development timeline risks making these challenges even more significant; therefore addressing critical policy and financing issues will be key to enable a functioning, agile and networked global ecosystem capable of delivering the 100-day aspiration.

Cross-ecosystem collaboration, legislation and financing

A robust global architecture for pandemic preparedness and response capable of achieving the 100-day aspiration will require strong partnerships underpinned by effective and agile legislative and governance frameworks that facilitate cooperation, financing and data sharing. Initial steps to accomplish this goal will need to focus on achieving better alignment of resources and stakeholders across the vaccine development pathway to improve coordination and enable system readiness.

Alignment of stakeholders, roles and governance

Establishing and strengthening partnerships and clearly defining roles and responsibilities across the broader ecosystem ahead of the next pandemic will enable accelerated emergency vaccine development. Critical elements of a more effective collaborative preparedness and response ecosystem will include establishing a **global accord on pandemic prevention, preparedness and response**[65] including a description of governance between countries for equitable access; establishing **clarity on roles, responsibilities and communication pathways** among diverse stakeholders across the ecosystem;

65 WHO, 2021. World Health Assembly agrees to launch process to develop historic global accord on pandemic prevention, preparedness and response.

mapping, **supporting and maintaining stakeholder networks** across key areas of the vaccine development value chain, including assay development, clinical evidence generation, manufacturing and supply, regulatory, procurement and distribution; and clarifying rules of the road and alignment points across these key areas by identifying interdependencies and minimising hand-offs.

Pre-established international legislation

Firm commitments must be enacted to build a political superstructure for mutual security and to protect the most vulnerable. Governments will need to help drive the legal framework necessary to achieve this, such as through the **global accord on pandemic prevention, preparedness and response; strengthening of the International Health Regulations**[66]; and the **establishment of a Global Health Emergency Council**[67]. Throughout the establishment of new mechanisms and the evolution of existing ones, precautions must be taken to ensure appropriate global representation and inclusion from all regions and help mitigate fragmentation. It is also vital that these mechanisms are coordinated and complementary to each other to avoid duplication and increase efficiency.

At-risk financing framework

Many of the scientific and technological innovations presented in this report require at-risk financing of products and activities that may not be relevant in the short-to-mid-term but would need to be prepositioned in order to be prepared for the next pandemic. Sustainable funding during interpandemic periods is required to allow the necessary **long-term investments in preparedness**, as well as **ready-releasable surge financing** to respond immediately to new outbreaks. The latter must include mechanisms for **financing R&D response activities, manufacturing 'at-risk' and advanced purchase agreements** to incentivise R&D and manufacturing and facilitate equitable access, particularly for outbreaks that initially occur in lower-income regions. In the event of an outbreak, transparent and pre-negotiated triggers would need to be in place to release funding for immediate initiation of activities to achieve the 100-day development pathway.

Equitable access

The foundation of any effective global response to an outbreak depends on the ability to ensure equitable access by enabling vaccine availability for high-risk groups first independent of location and ability to pay. Several steps can be taken to encourage equitable access across a number of dimensions, including vaccine development and manufacturing target product profiles, financial and market incentives and contractual provisions. Examples include: establishing **mechanisms and governance for funding equal access to vaccines and therapeutics in lower-income settings** independent of ability to pay, including specific mechanisms for management of IP during an outbreak; ensuring that R&D activities contribute to enabling access **through readiness of platforms, dosing schedules and facilities for roll-out** in lower-income regions; funding to **increase country capabilities to run manufacturing facilities, clinical trials and post-authorisation surveillance**; and funding to provide **routine access to diagnostics and non-pharmaceutical interventions** to ensure continued monitoring, facilitate vaccine roll-out and help contain and control outbreaks.

Critical legal and liability challenges that could restrict fair global access also need to be mitigated, including by: putting in place **liability and indemnification and no-fault measures** across all member countries to facilitate rapid global roll-out; establishing a **global injury compensation** fund; prepositioning agreements on **barrier-free global supply chains for vaccines, raw materials and consumables**; and establishing **agreements on global allocation based on pre-defined criteria** (e.g., outbreak location, case rate, etc.).

66 WHO, 2022. International Health Regulations.

67 WHO, 2022. WHO Director-General's panel remarks at the Group of Friends of Global Health – 25 April 2022.

Call to action

Stopping or preventing the next pandemic, let alone in 100 days, is not something a single country or organisation can do alone. Nor will it be achieved by simply funding vaccine developers and biotech companies to advance innovative work. Success will likely require advancements in organisation, governance, and financing of global preparedness systems, and multiple, interconnected scientifically guided collaborative efforts. The 'moonshot' goal of making a vaccine against a new pandemic pathogen in 100 days is ambitious, but this research exercise shows it is not impossible.

Several organisations, including CEPI, have laid out ambitious programmes leveraging many of the approaches described in this paper. Other countries and regions have begun additional activities such as expanding vaccine manufacturing so that ready, prepositioned manufacturing capacity is less likely to be a limiting step in responding to the next pandemic.

CEPI'S approach

CEPI has a US$3.5 billion 5-year plan to help address the risk of pandemics and epidemics, potentially averting millions of deaths and trillions of dollars in economic damage. This plan will urgently address the critical remaining COVID-19 vaccine R&D gaps, including the immediate threat of COVID-19 variants to bring the COVID-19 pandemic to an end; and enable preparation to address future threats in a way which benefits the entire world.

The 100-day aspiration is directly aligned with CEPI's mission to radically reduce 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 during the COVID-19 pandemic, pushing forward the application of existing innovations or driving towards the critical preparedness prerequisites 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, regulatory authorities, academic and other public institutions, civil society organisations, and national governments to catalyse the critical conversations required for change.

More specifically, CEPI will work to achieve the 100-day aspiration by:

Strengthening defenses against COVID-19 and reducing the risk of future coronavirus pandemics, by filling the critical remaining R&D gaps that threaten to undermine the progress made in fighting the virus—including optimising of current vaccines, addressing variants of concern, and developing next-generation COVID-19 vaccines—and initiating the development of broadly protective or universal coronavirus vaccines.

Developing vaccines and other biologic countermeasures against known high-risk pathogens, to include advancing the development of vaccines for Chikungunya, Lassa Fever, Nipah, MERS and Rift Valley Fever; completing additional clinical trials to broaden the populations eligible for the Ebola vaccines; and commencing work on vaccines for additional priority pathogens with outbreak potential.

Producing a library of prototype vaccines against representative pathogens from critical viral families, to give the world a head-start when faced with novel threats. The library of prototype vaccines will leverage mRNA and other rapid response platforms to develop vaccine candidates that can be rapidly adapted if related viruses emerge.

Transforming and diversifying vaccine manufacturing so it is cheaper, faster, and closer to an outbreak, by investing in manufacturing innovations; supporting LMICs to develop sustainable manufacturing capacity; and contributing to the establishment of a global manufacturing coalition to respond to outbreaks.

Advancing enabling science programmes which are critical to the success of rapid vaccine development, including developing biological assays, preclinical models, epidemiological studies, and diagnostics for priority pathogens; and building clinical trial capacity.

Enabling equitable access to life-saving vaccines, by leveraging CEPI's R&D investments to enable access to the tools that CEPI also fund; supporting LMICs to take ownership of their national health security; and advocating for the design of a global pandemic preparedness and response system founded on the principles of equitable access.

Appendices

Appendix I Methodology

This research exercise deployed a mixed-methods approach.

First, was an initial review of the historical experience from pre-COVID vaccine development, benchmarking against a reference set of vaccines for four pathogens (recombinant zoster vaccine for herpes zoster (Shingrix), 9-valent HPV vaccine for human papilloma virus (Gardasil 9), pneumococcal 7-valent conjugate vaccine (Prevnar septavalent) for pneumococcal infections, and Ebola Zaire vaccine (Ervebo) for Ebola virus disease), using data in the public domain, including publications[68,69], company press releases and clinicaltrials.gov data.

A similar process was used to plot the development and manufacturing timelines of COVID-19 vaccine candidates from developers that, at the time, either were approved by a stringent regulatory authority or had been issued with an Emergency Use Listing (EUL) by the WHO (AstraZeneca/Serum Institute of India, Bharat Biotech, CanSino Biologics, Gamaleya Research Institute, Johnson & Johnson, Moderna, Novavax/Serum Institute of India, Sinopharm, Sinovac). The start of vaccine development was defined as the day when the COVID-19 sequence was made available (January 11, 2020) and the endpoint for each vaccine candidate was defined as the date when emergency use authorisation (EUA) or conditional approval was granted by a stringent regulatory authority or emergency use listing (EUL) by WHO.

As a second step, a consultation of stakeholders involved was organised. Interviews with 58 vaccine experts were requested. Forty-nine of these requests received a positive response (84%), of which 46 were conducted to date. These interviewees included representatives from vaccine developers (23), international institutions (12), regulatory agencies (8), academia (2) and media (1). In all cases, timelines and innovations used were confirmed and ideas relating to further optimising the development processes and how the 100-day goal could be achieved were solicited. These insights and ideas were combined with an analysis of best practice timelines, focusing intensively on the three vaccines with the earliest FDA or European Medicines Agency (EMA) regulatory approval (Pfizer-BioNTech, Moderna and AstraZeneca). A team of CEPI-employed scientific and vaccine development experts reviewed each of the timelines, coming to a consensus about potential time savings and a theoretical minimum timeline that could be achieved in the future.

The theoretical minimum and 100-day timeline ideas were validated through repeat interviews. Based on the interview process, literature research, and internal analysis the following outputs were assembled: (1) a catalogue of innovations that had been used during the pandemic, (2) innovations in use in other, non-vaccine-related therapeutic areas (e.g., oncology), and (3) innovations partially applied to the development of COVID-19 vaccines. The final output is a representation of important paradigm shift prerequisites and enabling innovations for consideration.

This research and analysis are subject to several important limitations. First, it is focused on the trajectory of vaccine development and manufacture during the COVID-19 pandemic. Timelines for all COVID-19 vaccines under development were not studied, and hence other important innovations may have been omitted. The estimates of time savings are predominantly based on interviews with industry experts and not on direct observation of development processes. They also depend on the tight synchronisation of discrete processes, which is unlikely to happen spontaneously and will require very significant preparation. A holistic assessment of the trade-offs between safety and efficacy was not the primary objective and a full assessment of those trade-offs in varying risk contexts is needed.

68 Agrawal, G. et al., 2021. Fast-forward: Will the speed of COVID-19 vaccine development reset industry norms?

69 Wolf, J. et al., 2020. Applying lessons from the Ebola vaccine experience for SARS-CoV-2 and other epidemic pathogens. npj Vaccines, 15 June, Issue 5, p. 51.

Appendix II Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
BARDA	Biomedical Advanced Research and Development Authority
CDMO	Contract development and manufacturing company
CEO	Chief Executive Officer
CEPI	Coalition for Epidemic Preparedness Innovations
CFR	Case Fatality Rate
CHIM	Controlled Human Infection Model
CGD	Center for Global Development
CMC	Chemistry, Manufacturing, and Controls
COVAX	COVID-19 Vaccines Global Access
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organisation
EMA	European Medicines Agency
EUA	Emergency Use Authorization
EUL	Emergency Use Listing
eQMS	Electronic Quality Management System
FDA	Food and Drug Administration
FIH	First-in-human studies
GMP	Good Manufacturing Practice
HPV	Human Papillomavirus
ICMRA	International Coalition of Medicines Regulatory Authorities
IP	Intellectual Property
LICs	Low-Income Countries
LMICs	Low and Middle-Income Countries
MCM	Medical countermeasures
MERS CoV	Middle East Respiratory Syndrome Coronavirus
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	Messenger ribonucleic acid
NHRVR	National Healthy Volunteer Research Register
PAES	Post-authorisation effectiveness study
PASS	Post-authorisation safety study
QMS	Quality Management System
R&D	Research and Development
R&D&M	Research & Development and Manufacturing
RNA	Ribonucleic acid
RWE	Real World Evidence
SARS-CoV-1	Severe Acute Respiratory Syndrome Coronavirus 1
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOP	Standard Operating Procedures
UK	The United Kingdom
UNICEF	The United Nations Children's Fund
US/USA	The United States of America
WHO	World Health Organization

Appendix III Innovations Catalogue

Status of innovation implementation
(i.e., has this innovation been used before to accelerate vaccine development timelines?)

Implemented	Partially Implemented	Future Potential

Impact of innovation

High	Medium	Low

Development Stage	#	Innovation	Description	Status	Impact		
					Timeline	Access	Scale
Sequence availability, candidate development and preclinical	1	Investment into pre-establishing vaccine platforms	Investment in priority platforms with rapid modifications for new antigens (e.g., mRNA, viral vectors) Financial models to incentivise companies to develop diverse platform technologies as single ones are unlikely to work for all viruses				
	2	Early vaccine adjuvant selection	Partner with adjuvant manufacturers to evaluate suitability of a range of well characterised adjuvants for the selected vaccine technology or antigen				
	3	Animal models for priority pathogens	Animal models against priority pathogen that can be quickly adapted for use with related pathogens				
	4	Development of assays including multiplex assays to minimise assay	Development of multiplex assays that are ready for use across a viral family Development to greatest extend possible prior to outbreak of essential assays for vaccine development and manufacturing (immune response assays and reagents, release assays, process control assays and diagnostic assays)				
	5	Development of *in silico* models for vaccine characterisation	a) Immunogen: *In silico* models for immunogen selection and correlation with protection levels b) Animal studies: *In silico* trial activities to (partially) replace animal studies c) Clinical trials: Use of *in silico* models to (partially) predict likelihood of success of vaccine candidates in clinical studies to accelerate lead candidate selection and potentially dosing				
	6	Generation of viral family prototype vaccines	Development of prototype vaccines against range of viruses in a virus family, using priority platforms. Preclinical and clinical data gathered ready for an outbreak				
	7	Use of computational models to expand viral family knowledge	Leverage previous research on antigen or disease and apply machine learning to predict disease characteristics of a viral family				
	8	Use of knowledge graphs	Collection and structuring of external and internal research data to facilitate hypothesis-generation relating to vaccine development				
	9	Faster at-risk decision-making	Improved organisational communication and delegation models to reduce delays between phases				
	10	Establishment of collaborative partnerships	Extended partnership between companies, and with public entities in research, development and manufacturing excellence/infrastructure Use of agreements to accelerate development and data availability				
	11	Funding commitments to support critical activities	Agreements with funding bodies on funding amounts released during different outbreak scenarios, including funding of development, manufacturing, and procurement				
	12	Active, continuous global surveillance to build database of pathogens and infections	Global surveillance of epidemic and/or infectious incidents to shorten reaction time (including technology innovations to enable tracking of outbreak spread in real-time e.g., via mobile phone use, social media platforms). Development of capabilities to locally collect isolates and sequence them				
	13	Non-clinical studies in parallel with clinical trials	Early commencement of clinical studies (in parallel to preclinical studies) based on pre-existing knowledge from platform experience				

Development Stage	#	Innovation	Description	Status	Impact		
					Timeline	Access	Scale
Clinical trials	14	Single-dose efficacious vaccine	Vaccine dose administered as a single shot conferring suitable levels of immunity; alternatively, evaluation of response after first dose and extrapolation to multi-dose regime				
	15	Immunobridging studies as proof of efficacy	Use of correlates of protection such as such as humoral and/or cellular immune parameters to predict protective response of vaccines against disease or death				
	16	Earlier robust biomarkers of immune response	Identification of correlates of protection or 'predictors or efficacy' to predict vaccine efficacy early on without the need to run large-scale event-based trials				
	17	Digital twin to support safety and efficacy studies	Use of comprehensive, longitudinal, clinical records created using baseline data collected from a subject before they receive their first dose to support clinical trials				
	18	National clinical trial and volunteer pre-registration	Pre-registration of volunteers and clinical sites (e.g., on national level) for future studies to achieve 100% enrolment on day 1. Potential pre-registration for Phase II/III studies				
	19	Prototype and platform specific dosing research	Based on platform data, reduce the need for Phase I dose finding studies and enable at-risk initiation of subsequent clinical studies. Models that allow safe dose finding predictions				
	20	Partnerships with Clinical Research Organisations	Effectively plan with CROs by reserving capability and capacity of experienced and ready to go clinical sites early on or pre-development, balancing inhouse and outsourced resources				
	21	Analytics driven trial site selection within global clinical trial networks	a) Optimisation of clinical trial footprint and site selection by using global incidence and disease monitoring to predict locations with maximal case loads b) Pre-defined clinical trial networks ready to be activated in countries and use of digital technologies to enable fast site start-up and engagement of health care professionals during pandemic restrictions				
	22	Real-time clinical trial monitoring and data transmission	Real-time, risk-based source data verification				
	23	Merged clinical trial phases	Based on platform data, pursuit of opportunities for greater overlap of clinical phases i.e., progression from Phase I to III by combining Phase I/II or II/III				
	24	Adaptive trial designs	Clinical trials where protocols can be adapted based on key parameters such as dose, safety, or efficacy incidence etc.				
	25	Use of prior platform safety data	Earlier decision-making based on platform understanding and knowledge, with continued extended safety monitoring using pharmacovigilance plans and real-world data				
	26	Masterfile for platform safety or vaccine component safety pre-approval	Regulatory Masterfile with integrated summary of safety experience for the vaccine platform.				
	27	Controlled human infection model studies	Consider CHIM studies for clinical proof of concept/approval based on benefit-risk				

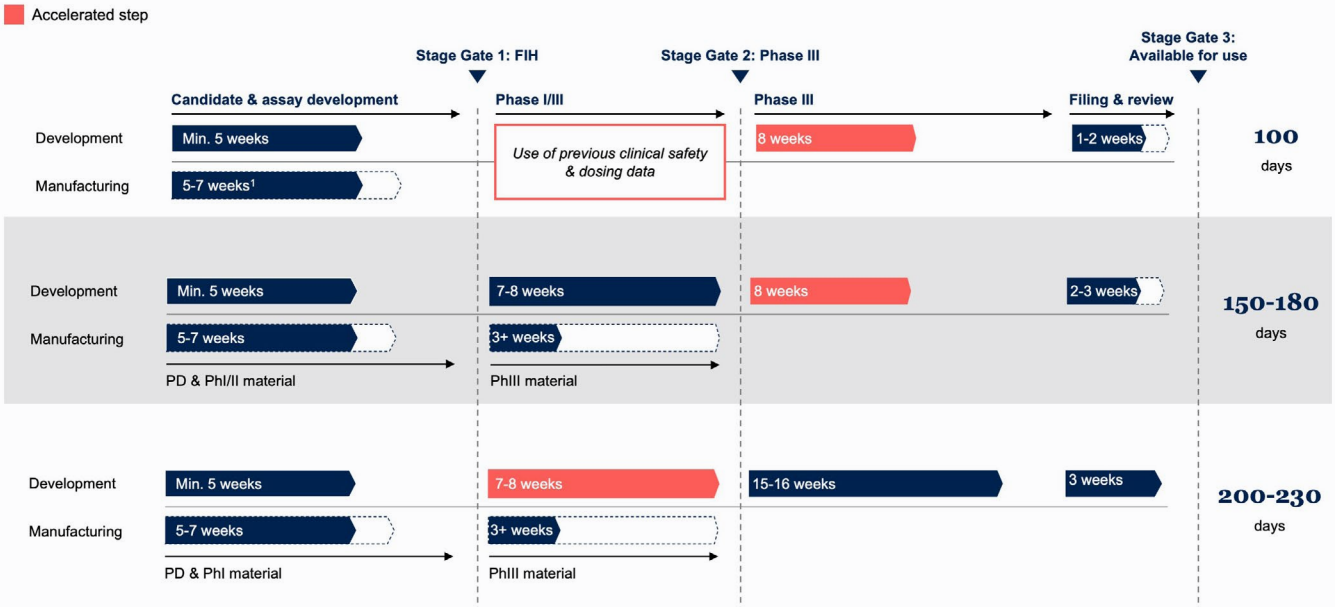
Development Stage	#	Innovation	Description	Status	Impact		
					Timeline	Access	Scale
Filing and approval	28	Pre-defined standards for post-authorisation studies	Clear upfront guidance on requirements for post-authorisation safety (PASS) and effectiveness (PAES) studies, e.g., RWE. Linked to harmonised trial designs and ensures efficient trial setup during outbreak				
	29	Continuous developer-regulator communication	Early and frequent communication and engagement including real-time data review, between companies and regulators establishing faster feedback loops				
	30	Rolling data reviews	Continuous review around new data beyond pre-defined submission deadlines and accelerated review timelines				
	31	Rolling shelf-life review	Regulatory approval without extensive stability studies upfront by using manufacturing date and later submission of evidence as it becomes available to specify shelf-life Use of 'date of manufacture' rather than 'expiry date' while shelf-life review occurs				
	32	Aligned requirements between regulatory authorities	Regulatory and ethics committee alignment and pre-approval of clinical trial designs and expected primary. Use of clinical trial protocol templates that can be rapidly adapted by developers Harmonisation of definitions and data requirements and sharing of information between different regulatory authorities. Agreement between regulatory agencies and developers to enable sharing of information between regulators.				
	33	Accelerated approval for use	Emergency authorisation based on interim data and smaller number of accrued cases provided sufficient safety data are available				
	34	Vaccine roll-out in consenting populations	Following safety studies in Phase I and II trials, vaccines are rolled out for use in consenting target populations while controlled efficacy studies ongoing				
	35	Pre-defined benefit-risk emergency authorisation pathways	Agreement with regulators on emergency authorisation pathways and requirements under different benefit-risk scenarios Developers could liaise with regulatory agencies to pre-define acceptable trial design and endpoints				
	36	Pre-programmed CFR and benefit-risk models	Computational models to reliably extrapolate case fatality rate of novel outbreaks based on multiple parameters to support the determination of the applicable benefit-risk profile				

Development Stage	#	Innovation	Description	Status	Impact		
					Timeline	Access	Scale
Manufacturing	37	mRNA printers	Automated micro-factories that can process desired batches of RNA molecules wherever installed				
	38	Thermostable vaccines	Vaccine platforms or formulations with increased heat stability allow easier formulation and faster distribution to increase equitable access				
	39	Pre-optimisation of manufacturing processes and rapid release assays for accelerated availability of commercial and clinical supply	Early use of GMP materials during preclinical process development to avoid later changes and use of optimised platform and technology transfer process to enable accelerated commercial production				
	40	At-risk clinical or commercial scale manufacturing	Manufacturing of commercial material started with at-risk financing (e.g., during clinical or preclinical phase, based on platform manufacturing experience)				
	41	Parallel development, scale-up and technology transfer	Process optimisation for pathogen-adapted prototype vaccines alongside implementing scale-up capabilities and assay development				
	42	Optimisation of emergency manufacturing capacity	Operational plans for emergency manufacturing capacity to be activated quickly for vaccine development				
	43	Continuous manufacturing suites	End-to-end manufacturing systems as compared to batch manufacturing, that can process starting material to finished product without intermediate stopping steps				
	44	Scenario-specific CDMO contracts	Contracts for pre-reserved CDMO capacity that can be activated in case of an outbreak				
	45	Developer-instituted cloud-based quality management system	Developers cloud-based eQMS systems applied to CDMOs and across facilities to unify and control documentation processes, batches and data capturing				
	46	24/7 operations	Switch to 24/7 shift work, e.g., manufacturing plants, candidate development				
	47	Modelling and forecasting of supply chain needs and potential disruptions	Link transmission modelling predicting vaccine demand with supply chain modelling to ensure supply of raw materials and vaccine				
	48	Overcoming consumable supply limitations	a) Creation of a consumables marketplace b) Improved demand signal given to consumable suppliers c) Diversify and safeguard vaccine and consumable manufacturing for equitable use				
	49	Standardisation of consumables and supply chain redundancy	Prototype manufacturing SOPs using a wider range of approved raw material suppliers or reusable consumables or pre-approved consumable substitutions to avoid supply chain bottlenecks				
	50	Remote manufacturing site inspections	Inspections carried out remotely and regularly on manufacturing sites to foster quality mindset. Sites should aim to be in a state of continuous GMP readiness				

Appendix IV Case Study

The scenarios below describe different paths for vaccine development once an outbreak is declared.

Three scenarios for response to an outbreak of a novel pathogen



The **100 days scenario** could be achieved under circumstances where vaccine development consists of the adaptation of a well-understood prototype vaccine candidate into a new, pathogen-specific vaccine (e.g., SARS-CoV-3). The high similarity to a prototype vaccine – as this would be a new strain of the now well-studied SARS Coronaviruses – and the existence of a defined high-risk group would open a path to developing a vaccine in 100 days.

In the case of a vaccine against a virus for which a related prototype vaccine does not exist, the degree of familiarity with the target – whether intermediate, or low – would dictate the length of the development process – a scenario in which the vaccine might be available in **150-180 days**, or one where availability would require at least **200 days**, respectively.

The timeline for accelerated emergency vaccine development and authorisation will depend on the answer to two critical questions:

Scenarios / Questions	Can Phase I/II trials be replaced with previous data on platform and prototype safety and dosing?	Can Phase III studies be shortened to single-dose event-based trials or can efficacy be shown with animal immunobridging models alone?
100 days	YES	YES
150-180 days	NO	YES
200-230 days	NO	NO

In all three scenarios, **candidate development** through antigen design would be relatively straightforward, building from knowledge accumulated during the development of prototype vaccines on rapid response platforms (e.g., mRNA). Assay development would occur by leveraging serum collection networks and adapting and optimising from existing prototypic multiplex assays. Manufacturing of large-scale clinical batch would be initiated in these early weeks, and in some cases, it might even be possible to begin commercial manufacturing in 'warm' facilities. *This analysis suggests that these* ***immediate reaction*** *activities, including manufacturing, could take place in 5-7 weeks.*

The key area of divergence in vaccine development timelines amongst the three scenarios would occur in the **Evidence Generation and Filing** phases.

In the **100 days scenario, evidence generation** would follow an accelerated timeline made possible by leveraging existing clinical safety and dosing data. Indeed, under the right circumstances, a path could open to proceed straight to Phase III studies, using pre-existing prototype and platform vaccine dosing information to select one or two doses for evaluation. This approach would only be possible in situations where there is clarity on platform versus antigen safety signals, high confidence in antigen safety, and a high level of confidence in safety and efficacy of dosing. **Phase III studies** could be based on single-dose event-based trials organised through the rapid enrolment of a large number of volunteers in a pandemic situation, or through clinical immunobridging trials whereby correlation between nonhuman and human immune response is used to indicate efficacy. *In the best-case situation, Phase III trials could be achieved in 8 weeks. Even faster timelines could be achieved by omitting Phase III trials if there is a potential for significant benefit to high-risk groups.*

In the **150-180 days scenario**, it would not be possible to replace Phase I/II trials with previous data on platform and prototype safety and dosing. That said, in the case of a global pandemic with high case numbers in different locations, it would likely be possible to generate evidence through **merged Phase I/II trials** to test safety and optimal dose in smaller patient populations by using more limited pre-existing safety and dose-finding data from prototype vaccines to inform trial design. *This could take place in 7 to 8 weeks, while manufacturing of additional clinical material occurs concomitantly in about three weeks.* Efficacy evidence generation could be accelerated through **single-dose event-based Phase III** making use of the rapid activation of clinical trial networks to quickly enrol thousands of participants. Trial size reduction may be possible by using **CHIM studies**, but this would only be suitable for low CFR scenarios which are difficult to reliably quantify in the early days of an outbreak. *In the best of cases, such Phase III trials would require 8 weeks or less.* A timeline of 8 weeks would consist of large-scale enrolment taking place in 1 to 2 weeks, a minimum of 2 weeks between vaccination and starting to count infections, time until symptoms arise (which is highly pathogen dependent) would take a minimum of a week, 2 weeks or more until hospitalisation endpoint, and finally, about 1 week for data analysis.
A timeline of 150-180 days could also be achieved with **Phase III clinical immunobridging trials** and the use **computational and *in vitro* models** to quickly adapt in vivo animal models to novel pathogens. This would only be possible if there exists **regulatory acceptance** of *in vivo* animal model correlation with human protection. Here too, *the timeline could take place within 8 weeks*, but might last longer depending on the type of animal model available and need for model optimisation.

Under the **200-230 days timeline scenario**, it would not be possible to replace Phase I/II trials with previous data on platform and prototype safety and dosing, nor shorten the timeline to Phase III studies. In this scenario, **merged Phase I/II trials** as described above would likely precede two-dose event-based Phase III trials. These will leverage innovations such as the use of **a Masterfile for safety of platform and vaccine components** to enable omission of Phase I completely, or a reduction in the datasets required to move to Phase II due to the prior safety data available from **prototype-specific dose and dosing frequency research**. *The merged Phase I/II trials would take 7-8 weeks* including up to 1 week for enrolment (also enabling dosing in sequential cohorts to check for acute adverse events), 3-4 weeks between administration of the two doses, immunogenicity testing 2 weeks after the second dose and up to 1 week for data analysis. *The two-dose event-based Phase III studies would take between 15-16 weeks following trial design with similar enrolment speed and scope as took place in COVID-19 trials.*

Finally, **filing** could take place through extensive use of platform data and formal acceptance of platform technology Masterfile, and continuous developer-regulator communication (including real-time data sharing) and rolling data reviews. In the 100 days scenario, this phase would take 1 to 2 weeks, but lead to a closely monitored **roll-out of the vaccine**. In the 150-180 and 200-days scenarios, **filing** would take longer and require about three weeks of review from regulatory authorities due to the lack of familiarity with the pathogen, and therefore greater need for safety and efficacy data.

As seen above, an accelerated timeline is possible as long as sufficient readiness investments and processes have been prepositioned, and reaction – through rapid outbreak characterisation, candidate and assays development – is immediate and follows a path towards rapid vaccine development. In many cases, regardless of the degree of familiarity with the pathogen (i.e., whether the pathogen is similar to another known pathogen in sequencing or molecular target), it would be most advantageous in terms of speed to assume that there is high-risk (in CFR, transmissibility, scale, location, etc.) and leverage the full range of innovations at hand to accelerate development timelines. As more and more information emerges about the pathogen and the outbreak, the approach could be adapted and higher-risk solutions replaced with more appropriate ones based on benefit-risk assessment.

There is also a scenario in which an outbreak would wane after a few months, potentially obviating the need for continued vaccine development efforts. Even so, initiating 'just-in-case' response efforts to achieve maximum acceleration of the timeline to vaccine availability would mitigate the risk of significant human and socio-economic impact and allow for testing whether established readiness infrastructure and processes are fit-for-purpose. Last, but not least, a 'just-in-case' response would enable the collection of additional data and information from vaccine and assay development, manufacturing, and evidence generation activities that could be leveraged to potentially accelerate response in the event of future outbreaks.

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