wellcome

COVID-19 Vaccines

The Factors that Enabled Unprecedented Timelines for Clinical Development and Regulatory Authorisation

GLOBAL HEALTH

Illustrations: storyset
Wellcome Trust, March 2022

Contents

Acknowledgements

Wellcome Trust developed this report as part of its continued efforts to improve the vaccine ecosystem and to support the research, development, and authorisation of vaccines. This project was supported by MMGH Consulting GmbH.

The project team warmly thanks the 88 experts who provided their time and valuable input through structured consultations in 2021. These experts spanned across 19 countries in all the World Health Organization regions, as well as, a variety of institutions and perspectives, including:

- Africa Centres for Disease Control
- African Union
- Agência Nacional de Vigilância Sanitária (ANVISA)
- AstraZeneca
- Bill & Melinda Gates Foundation
- Bharat Biotech
- Baylor College of Medicine
- Coalition for Epidemic Preparedness Innovations (CEPI)
- CSL Limited
- CureVac N.V.
- Daiichi Sankyo Company, Limited
- Duke University
- European Medicines Agency
- Gavi, the Vaccine Alliance
- Imperial College
- INCLEN Trust International
- Indian Immunologicals Limited
- International Vaccine Institute
- International AIDS Vaccine Initiative (IAVI)
- Johnson & Johnson
- Kenya Medical Research Institute (KEMRI) Wellcome Trust Research Programme
- Serum Institute of India
- PATH
- Pfizer Inc.
- PsiOxus Therapeutics
- Sanofi Pasteur
- University of Oxford
- Wits Reproductive Health and HIV Institute
- World Health Organization, headquarters and regional offices

Their contributions resulted in the identification of key actions that leverage the current momentum for COVID-19 vaccines towards improving the vaccine ecosystem to support more efficient development and authorisation of vaccines against deadly diseases.

Executive summary

Objective and methodology

Historically, clinical development and approval of vaccines have spanned approximately 10 years with only ~16% of vaccine candidates ever receiving market authorisation.[1, 2, 3, 4, 5] The long timelines and the low success rates are the product of the complex ecosystem where each vaccine candidate faces multitudes of challenges.[6] However, the SARS-CoV-2 pandemic overcame many of these historical challenges, and within 12 months of the detection of the first SARS-CoV-2 case, at least six vaccines had received emergency use authorisation. Further, as of December 2021, just two years following the detection of the first SARS-CoV-2 case, there are 28 vaccines that have been approved by at least one country.[7] This rapid pace to develop and authorise COVID-19 vaccines raised the question of whether any of the actions employed to develop COVID-19 vaccines could be replicated for vaccine development in the future. The Wellcome Trust sought to **identify and understand the impact of the different factors that enabled the rapid clinical development and emergency use authorisation of COVID-19 vaccines to take forward any lessons learned to improve the vaccine ecosystem for future vaccine development, for pandemics, epidemics of emerging pathogens, and endemic diseases.**

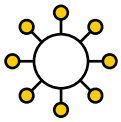
This research builds on the prior research conducted on the vaccine ecosystem, which identified 10 barriers that impacted the time to market for vaccine candidates. It focuses on exploring the contextual changes and actions that accelerated COVID-19 vaccine development and authorisation timelines. To achieve the stated research objective, this research utilised a mixed-methods approach, combining a review of 683 published and unpublished literature articles, consultations with 88 experts, and quantitative analyses.

Identified factors impacting vaccine development and authorisation timelines

This analysis resulted in the identification of 32 factors that impacted the development and authorisation timelines of COVID-19 vaccines. The factors were organised into four areas: (i) the pandemic context – significant health, economic, and social impacts leading to high political will; (ii) the unprecedented financial investment – contributed to more efficient decision-making for clinical trial sponsors; (iii) the proactive regulatory approach – a prioritisation of human resources and increased collaborations; and (iv) the faster clinical development – the availability of existing research and outputs and streamlined processes for COVID-19 vaccine clinical development.

The figure on the following page provides an overview of the interaction of the factors and their impact on COVID-19 vaccine development and approval timelines.

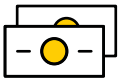
Interaction and impact of key factors on COVID-19 vaccine development and approval timelines



1 Pandemic context

The massive toll on economies, society, and health, particularly in high income countries, triggered strong political will and pressure to act that changed the risk-benefit assessment for key stakeholders.

Risk-benefit assessment



2 Unprecedented financial investment

Financial investments and advance purchase agreements on a massive scale, comprised of unparalleled public investment, supported all elements of vaccine research and de-risked development.

3 Proactive regulatory approach

The prioritisation of human resources resulted in increased collaboration with developers particularly in countries of origin and additional flexibility in the timing of data requirements and the timing of review processes.

4 Faster clinical development

The availability of existing research and its outputs

Decades of vaccine research and development on vaccine platforms, coronaviruses, and structural biology of protein antigens were immediately available and used.

Streamlined clinical development processes

The re-allocation of human resources by vaccine developers, the financial de-risking, and regulatory flexibility allowed rapid decision making and the ability to conduct clinical trial steps in parallel, rather than sequentially.

The pandemic context – the significant health, economic, and social impacts leading to high levels of political will

One consistently identified factor of the SARS-CoV-2 pandemic was the **significant health, economic, and social impacts** experienced worldwide, including in high-income countries. By the end of 2020, there were over 1.8 million reported deaths and an estimated excess mortality of at least 3 million persons.[8] The pandemic's health impact did not slow down, as by December 2021, the global number of deaths more than doubled to over 5 million deaths.[9] In April 2020, the International Monetary Fund projected that the global economy would contract by -3%, which was worse than the 2008-09 financial crisis, and it flagged the high risk for even more severe economic outcomes.[10] During this time, many countries were already in lockdown, which heavily impacted daily life, potentially increasing inequities within countries as well as having other potential impacts related to educational outcomes, mental health, and domestic violence.[11, 12]

This factor drove the behaviours and actions of all key stakeholders and created additional factors that had a significant impact on the vaccine development and authorisation timelines. For example, the significant health, economic, and social impacts resulted in **high levels of political will and a sense of urgency**. This increased the risk appetite of political stakeholders and led to the **high levels of financial investments** and the **high prioritisation of human resources** towards the development and authorisation of COVID-19 vaccines. Further, the changed risk-benefit assessment led to more **rapid decision-making** during the clinical development and a more **proactive approach from regulatory agencies**. Finally, the SARS-CoV-2 context created **more opportunities for partnerships and collaboration, and there was an openness to share research outputs**, which influenced vaccine design as well as the ability to develop and commercialise COVID-19 vaccines.

Unprecedented financial investment – contributed to more efficient decision-making

The **unprecedented size of financial investments from multiple funding sources** made towards COVID-19 vaccine clinical development and the advance purchase agreements between governments and pharmaceutical companies were identified as two key factors that impacted the timelines. Together, both factors helped to **de-risk the clinical development, as a candidate's financial burden and risk of failure were shared amongst multiple stakeholders, ultimately resulting in faster decision-making and a streamlined clinical development process**. This highlights that there was a commitment to finance the vaccine development regardless of the risks and before the key results were known, thus, enabling many vaccine candidates to progress quickly through the clinical development process compared to a non-pandemic context.

Linked to the above two factors, there was an **unprecedented level of demand for COVID-19** vaccines to address the SARS-CoV-2 disease burden, given the absence of other pharmaceutical interventions. This level of demand contributed to the **pooling and coordination of funding** to support both COVID-19 vaccine development and the **creation of an attractive global market** for approved vaccines. Finally, the consultations revealed that the **early engagement and financing provided by organisations focused on emergencies**, such as Coalition for Epidemic Preparedness Innovations (CEPI) and Biomedical Advanced Research and Development Authority (BARDA), played a role in accelerating timelines for clinical development and removing some of the initial barriers faced by vaccine developers. The identified financial factors accelerated COVID-19 vaccine development largely by substantially accelerating the management approval of candidate vaccines and **allowing for clinical research and development activities to be conducted in parallel** rather than sequentially.

Proactive regulatory approach – prioritisation of human resources and increased collaborations

From the outset, regulatory authorities in countries of origin[1] articulated the key data requirements that would enable **emergency use authorisation**, which helped to support rapid access to vaccines shown to be effective in clinical trials. On this basis, **regulators advised vaccine developers about the minimum clinical, non-clinical, and manufacturing data** required to support the regulatory reviews and approvals of candidate vaccines. Thus, clinical trial protocols were able to be designed to generate the necessary evidence required. The safety and efficacy of candidate vaccines were the two highest priorities for regulators in countries of origin when assessing vaccines for emergency use.

While aligning on the requirements was important, consultations also highlighted that the **immediate and ongoing collaboration with regulators** was instrumental in improving timelines. In addition to the upfront decisions that regulatory authorities took to define the data required to support emergency authorisation, regulators in countries of origin also took several critical process-related actions, such as **prioritising COVID-19 reviews over other non-SARS-CoV-2-related health products, allowing flexibility in the sequencing of submission and review, and conducting rolling reviews**.

While many praised regulators' level of collaboration and prioritisation, this may not be fully replicable in a non-pandemic environment due to the need to spread regulatory resources, expertise, and experience across a range of health topics. Further, it is important to note that regulators' prioritisation of COVID-19 interventions had a negative impact on the pharmaceutical interventions of other diseases during the pandemic and put significant pressure on staff workload and morale.

The findings from this research indicate that the regulatory review and process for first authorisation was done in an efficient manner largely due to the level of experience and expertise of the stringent regulatory authorities. However, the regulatory review and process by countries of use faced more challenges. First, many countries did not have emergency use authorisation processes in place but have taken this opportunity to develop these processes. Second, while **regulatory harmonisation and reliance**[2] was used and resulted in some efficient authorisations in countries of use, consultations found there is a need to continue to improve harmonisation and reliance mechanisms. One potential factor that positively impacted the regulatory review and process in countries of use was the **use of inclusive forums for open, transparent discussions**.

Faster clinical development – the availability of existing research and outputs and streamlined COVID-19 vaccine clinical development processes

Nine factors related to clinical development advancements and practices were identified. These factors could be divided into two subgroups: (i) the scientific advancements already made in vaccine research and development that were not specifically related to the SARS-CoV-2 pandemic, and (ii) streamlined clinical development processes for COVID-19 vaccines. Two factors falling into the first subgroup include the **decades of prior research performed to develop new vaccine platform technologies** (e.g., mRNA and non-replicating viral vectors), and the **prior research and development activities on coronaviruses with pandemic or epidemic potential** (e.g., SARS-CoV-1 and MERS). The technology of new vaccine platforms was essentially at a stage where it could be immediately leveraged for COVID-19 vaccine development, and the prior research and vaccine development activities due to the SARS-CoV-1 and MERS outbreaks armed the vaccine developers with a strong understanding of the SARS-CoV-2 structural biology, mode of transmission, and areas of the virus to target for a

1. Country of origin is defined as the country where the initial dossier for authorisation of COVID-19 vaccines was filed.
2. Regulatory reliance refers to the act whereby the regulatory authority in one jurisdiction may take into account and give significant weight to (i.e., totally or partially rely upon) evaluations performed by another regulatory authority or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others.

strong immune response (e.g., the spike protein). The prior research on the optimal immunogenic targets for coronavirus vaccines and the readiness of new vaccine platform technologies enabled COVID-19 vaccine candidates to be designed for pre-clinical and subsequent clinical testing more quickly than the historical precedent.

The second subgroup of factors relates to a more streamlined process used for COVID-19 vaccine clinical development. Due to the scale of financial investments, clinical development was de-risked due to the sharing of financial burden, which accelerated **decision-making and allowed clinical trial steps to be conducted in parallel**. Further, when vaccine candidates were ready for human testing in Phase I/II/III trials, the clinical trials were designed as **consolidated phases** and conducted in countries or sites that had **strong and flexible research capacity and clinical trial infrastructure as well as high burden of SARS-CoV-2**.

Translating lessons learned for action and investment

The SARS-CoV-2 pandemic highlighted the incredible possibilities and impact when barriers to vaccine development and authorisation were addressed. These lessons learned have the dual advantage of better preparing for a future pandemic as well as creating a more efficient approach towards vaccine research, development, and regulatory processes for epidemic and endemic diseases.

The SARS-CoV-2 pandemic highlighted the importance of laying the groundwork and foundation to ensure rapid vaccine development and authorisation. COVID-19 vaccine development benefited greatly from decades of scientific research and development; thus, it is important that there remains continued funding towards scientific advancements and structural biology as well as implementing smarter surveillance systems, improving data-collection processes and systems, appropriately training individuals in data analytics, establishing strong pathways to communicate data, and establishing strong clinical trial infrastructure in different regions.

For the epidemic and endemic vaccine development, experts identified key actions including ensuring the availability of funding for early phases and moving away from funding single vaccine candidates towards platform funding. Experts also stressed the role of regulatory forums to openly discuss issues between regulators, between regulators and key stakeholders such as vaccine developers, vaccine manufacturers and country policy makers. Such forums could also develop and release guidance documents or roadmaps (e.g., pilot an integrated multi-functional roadmap to provide scientific, process, and technical advice to clinical trial sponsors), provide opportunities to role-play situations, and serve to further build trust, ultimately contributing to regulatory harmonisation and reliance. Given that COVID-19 vaccine development benefited from decades of prior work on coronaviruses and vaccine platforms, experts highlighted the need to continue work on vaccine platforms as well as building out research streams on specific virus families. Finally, due to the challenges faced during COVID-19 vaccine development, the experts identified actions related to having established animal models for key diseases, ensuring sufficient manufacturing capacity to produce clinical trial materials, and generating data from various pathogens on different vaccine platforms as being important actions to improve the ecosystem.

Call to action

The SARS-CoV-2 pandemic triggered concerted action by governments, funders, regulators, and industry that overcame many of the historical challenges that vaccine candidates usually face during the development and authorisation process. These challenges include financial, regulatory, manufacturing, clinical, market and policy barriers.

Action to remove these barriers resulted in six highly effective COVID-19 vaccines being safely developed

and authorised for use in less than one year, 10 times faster compared to the average timelines for developing vaccines for other infectious disease threats.

We call on governments and funders to learn from the lessons of the SARS-CoV-2 pandemic and take the following actions to build a more efficient and effective vaccine ecosystem that can protect us from other pandemic, epidemic, and endemic disease threats.

1. **Commit sustained financial support for scientists and foundational science** for the full vaccine design and development process, prioritising investment in:
    - Understanding pathogen biology including structural biology.
    - Developing predictive model systems for key diseases.
    - Advancing rapid, flexible vaccine technology platforms such as mRNA and viral vectors.
2. **Establish strong clinical trial infrastructure** in regions of infectious disease burden
    - Ensuring sufficient manufacturing capacity is available to produce vaccine doses for clinical trials.
    - Building sustainable research capacity to conduct vaccine trials.
    - Building regulatory capacity in countries of highest disease burden to support, conduct, and approve clinical trial processes.
    - Implementing smarter surveillance systems, improving data-collection and data-sharing systems, increasing data analytics capacity, and using such data to inform clinical trial design for vaccine efficacy and effectiveness studies.
3. **Support and strengthen global funding mechanisms** to de-risk and advance development of vaccines for pandemic and endemic diseases, including:
    - Meeting CEPI's $3.5 billion replenishment target to support its mission to condense new vaccine development timelines for pandemic disease threats to 100 days.
    - Identifying effective funding mechanisms to support early-stage R&D for key endemic diseases and guarantee demand for such vaccines to ensure successful development.
4. **Facilitate communication** between regulatory authorities and other stakeholders by developing forums for:
    - Promoting open discussion between regulators in different regions and support regulatory harmonisation and capacity development.
    - Promoting open discussion between regulators and vaccine developers and between vaccine developers, manufacturers, and policymakers in countries of use.
    - Developing and releasing comprehensive guidance documents and provide opportunities to role-play situations.

As the world considers how it can strengthen its response to major infectious disease threats in the future, it is critical that we learn from the SARS-CoV-2 pandemic and invest in the necessary infrastructure to improve capacity, efficiency, and success in the development of vaccines for other infectious diseases. By committing to sustainable investment in research, strengthening clinical trial infrastructure, de-risking vaccine development, and facilitating better communication between regulatory authorities and other key stakeholders, we can help build a world that is better prepared to prevent and eliminate infectious diseases.

About this research

Research goal

Historically, clinical development and approval of vaccines have spanned approximately 10 years, with only ~16% of vaccine candidates ever receiving market authorisation.[1-5] The long timelines and the low success rates are the product of the complex ecosystem where each vaccine candidate faces multitudes of challenges.[6] However, the SARS-CoV-2 pandemic overcame many of these historical challenges as within 12 months of the first detection of a SARS-CoV-2 case, at least six vaccines had received emergency use authorisation. Not only were vaccine candidates rapidly designed and evaluated in the pre-clinical phase to Phase I to emergency use authorisation in less than 12 months, but there were an unprecedented number, over 210, of COVID-19 vaccine clinical trials registered between February and December 2020 (Figure 1).[13]

This rapid pace to develop and approve numerous COVID-19 vaccines overcame many of the historic challenges in the ecosystem and raised the question of whether any of the actions employed to develop COVID-19 vaccines could be replicated for future vaccine development. Wellcome Trust sought to **identify and understand the impact of the different factors that enabled the rapid clinical development and emergency use authorisation of COVID-19 vaccines to take forward any lessons learned to future vaccine development for future pandemics, epidemics of emerging pathogens, and endemic diseases**.

This report provides an overview of the methodology, results, and recommendations, as well as a call to action for all key stakeholders to support a transformation of the vaccine ecosystem to enable more efficient development and approval of future vaccines for future pandemics, epidemics of emerging pathogens, and endemic diseases.

The findings from this report aim to take forward lessons learned from COVID-19 vaccine development and authorisation timelines and apply them to future vaccine development for pandemic, epidemic, and endemic diseases by assisting:

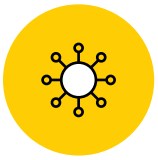
- **Vaccine researchers and developers** in defining innovative ways of working to efficiently reach research and development milestones.
- **Regulatory authorities** in identifying key lessons learned and actions that can positively impact the regulatory review process in countries of origin and use.
- **Financers of vaccine research and development** in prioritising funding towards specific actions that can influence vaccine development timelines and create efficiencies in the vaccine ecosystem.

Figure 1: Unprecedented number of COVID-19 vaccine clinical trials by country (February to December 2020) (n=217)

Research questions

Vaccine research, development, and authorisation operates in a specific ecosystem where the convergence and impact of several factors influence the timelines and success rates of vaccine candidates. A prior project identified a number of factors that impact the timelines and success rates of vaccine candidates.[6] They include disease burden and impact, research and development financing, clinical development processes, and regulatory environment. **We leveraged the prior analysis on the vaccine ecosystem to explore the contextual changes and actions that accelerated the COVID-19 vaccine development.** The objectives of this research were to identify the factors influencing timelines, determine which factors could be replicable in a non-pandemic environment, and prioritise key actions that could contribute to a more efficient vaccine ecosystem, ultimately resulting in faster development and market authorisation of vaccines for future pandemics, epidemics of emerging pathogens, and endemic diseases. The scope of this project was limited to pre-clinical to regulatory approval in countries of use. It does not explore factors impacting vaccine manufacturing or access to COVID-19 vaccines.

The research was structured to investigate four primary topic areas:



1. **The pandemic context**, including the high health, economic, and societal impacts, particularly in high-income countries, and the strong political will and prioritisation of resources towards COVID-19 vaccine development and authorisation.

2. **Unprecedented financial investments**, including the distribution of direct and indirect financing, such as early advance purchase agreements and significant public and private investments in COVID-19 vaccine development.

3. **Proactive regulatory review**, including the collaborative role that regulatory bodies played in the design and conduct of the clinical trials, the flexibilities in the submission and review processes, and the use of emergency use authorisation pathways.

4. **Faster clinical development,** including leveraging the historical work on coronaviruses and new vaccine platforms, the use of adaptive trial designs and collapsed trial phases, and the open sharing of research outputs.

Methodology overview

A mixed-methods research approach was adopted that leveraged the available literature, extensive stakeholder consultations, and quantitative analyses to achieve the research objectives. Figure 2 provides an overview of the key methods utilised to respond to the research questions.

First, a rapid assessment of peer-reviewed and public information sources from 1 January 2002 to 3 May 2021 was performed to identify potential factors. Journals, pre-print publications and other sources (e.g., websites, reports) were reviewed using detailed search terms. A total of 683 published and pre-print publications were reviewed in detail, and the relevant data and qualitative insights were aggregated for each identified factor. This literature assessment provided a preliminary understanding of the factors and their contribution to the acceleration of clinical development and approval timelines for COVID-19 vaccines. The results from the literature assessment were used to inform the consultations conducted.

Figure 2: Overview of project methodology

Literature appraisal

Identified all potential factors which may have impacted the timelines for COVID-19 vaccine development and approval.

Expert interviews

Online survey

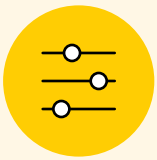
Validated the identified factors, determined the role and impact of each factor, and find any factors not identified in the rapid assessment of literature.

Focus groups

Prioritised factors based on replicability for future vaccine development and identified actions and investment to enable replicability

Factorial regression model

Identified the factors that correlated with progression through clinical development phases for currently licensed or candidate COVID-19 vaccines using WHO landscape of COVID-19 vaccine clinical trials



Comparator vaccines

Contextualised COVID-19 vaccine development timelines, financing and regulatory pathways against benchmark licensed and candidate vaccines – PCV, TB, H1N1

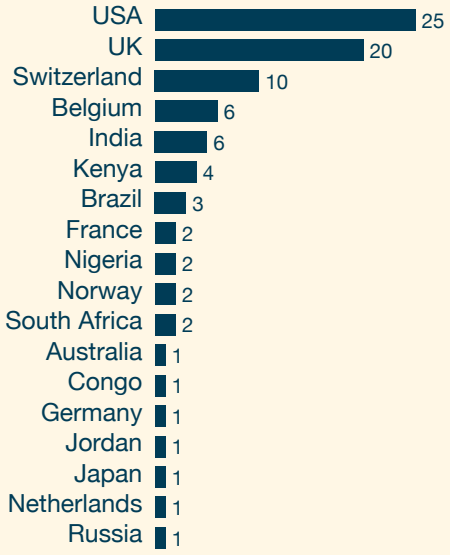
As a second step, a consultation using convenience sampling of 88 key stakeholders involved in the research, development, and regulatory review of COVID-19 vaccines was conducted through virtual interviews and an online survey, using the web-based software Qualtrics. The consultation aimed to validate the identified factors, understand the role each factor played, and identify any factors that may not have appeared in the rapid literature assessment. The feedback was consolidated and analysed quantitatively and qualitatively. Stratified analyses were performed on survey responses to evaluate differences in scoring by stakeholder groups. Figure 3 provides an overview of the individuals consulted by location.

Next, clinical development and regulatory experts were subsequently convened for two focus groups to validate the preliminary findings, prioritise the identified factors while considering their replicability for the development of future pandemic, epidemic, and endemic vaccine development, and brainstorm areas for action or investment to enable replicability.

In parallel, two additional analyses were conducted: (i) a two-level factorial regression model was conducted, and (ii) a comparison of COVID-19 vaccine timelines against other vaccines.

The two-level factorial regression model was conducted to identify factors that may correlate with the progression of COVID-19 vaccines. The model underwent an iterative design process and was refined to remove non-significant factors and associations. The factors reviewed included those that may have impacted the speed at which pilot-scale vaccines were available for testing, including the type of vaccine, the size of the collaborative group and the type of financing available, or the speed at which clinical trials were conducted, including the use of combination Phase I/Phase II, Phase II/III or Phase I/II/III trial designs, the experience of the regulatory agency overseeing the trials, and the experience and resources of the vaccine manufacturing company involved in the development. Source information for each factor evaluated in the model was identified through a targeted desk review of key sources of COVID-19 vaccine clinical trial information.

Figure 3: 88 individuals consulted by geographic location



COVID-19 vaccines were also evaluated against other licensed or in-development vaccines, comparing their timelines for clinical development and regulatory processes and the level of financial investments. The comparator vaccines were identified based on a selection framework using key epidemiological data related to a long list of potential vaccines and each vaccine was scored based on pre-defined thresholds. Based on this selection framework, Wellcome Trust selected the comparator vaccines.

Collectively, these data sources and analyses enabled both a quantitative and qualitative assessment of how each of the identified factors contributed to the rapid speed of COVID-19 vaccine development and regulatory processes, and which factors have the potential to be replicated to support future vaccine development for epidemic and endemic diseases.

Background and context

Overview of the vaccine ecosystem for vaccine development

Vaccine development is a long and arduous process that historically uses sequential steps starting with target product profiling and pre-clinical development. This is followed by a three-phase evaluation in humans and is finally concluded when regulatory authorities conduct a review of a submitted dossier. In 2020, Wellcome Trust commissioned research to (i) understand the vaccine ecosystem and the key decision points related to the vaccine research and development and the regulatory review process; and (ii) identify solutions that could optimise the ecosystem to reduce the burden of deadly diseases.[6] The ecosystem research focused on identifying challenges that impact vaccine development with a specific focus on their transition from Phase II clinical trials to the time of initial adoption in countries. As the research focused on the time after the transition into Phase II clinical development, it did not prioritise any scientific-related clinical development factors. Those factors are either resolved in earlier phases of clinical development or they lead to the discontinuation of the programmes. The report can be found here.

The ecosystem research resulted in **16 of 54 challenges being prioritised considering their impact on cost, time to market, and public health outcomes**. These 16 prioritised challenges span the topics of financial outcomes, regulatory, market and policy, and manufacturing. However, only 10 of those 16 priority challenges have an impact on the time to market for vaccines, hence they are the ones considered relevant for this analysis.

See Figure 4 for an overview of the 10 prioritised challenges identified in the vaccine ecosystem research that have an impact on time.

Overview of 10 prioritised challenges that impact time to market

While this pre-existing ecosystem research did not consider a pandemic lens, it provides important context on how the vaccine ecosystem operates and, in combination with the output of this research, highlights how the global response to the SARS-CoV-2 pandemic changed the vaccine development paradigm.

The identified financial challenges were often found to be the source of fundamental barriers to developing vaccines and ultimately increasing timelines to regulatory authorisation. Two main factors emerged as having a significant and direct impact. First, there is **limited availability of funds for the late-stage vaccine development**, particularly Phase III, which is the most expensive development phase due to the large enrolment requirements and long follow-up times. Thus, vaccine developers are forced to make decisions between vaccine candidates, which results in some viable vaccine candidates never progressing beyond Phase II. Second, **smaller vaccine developers and academic institutions may not be willing to conduct or be**

Figure 4: 10 prioritised challenges that impact development time from Phase II to licensure

Financial Outcomes

1 Limited availability of aligned partners to commercialise vaccine

Vaccine developers that do not have or are not interested in building capacity for licensure and commercialisation of the vaccine must find interested/capable partners that can commercialise the vaccine. The limited number of those partners can delay or hinder completely the availability of certain vaccines.

2 Insufficient access to funds for late-stage development

Phase 3 is the most expensive part of vaccine development. Very few small and mid-size developers can fully self-fund this development. This is especially true for companies based in emerging markets, where financial markets are less sophisticated and less interested in risky enterprises. This reduces the number of developers.

3 Lack of partners available/ capable of receiving technology transfer

Developers who are not capable of, or interested in, manufacturing their product require manufacturing partnerships for both clinical and commercial material. The general dearth of vaccine manufacturers globally and, in particular, of manufacturers capable of handling a specific technology, limits the potential for partnerships.

Regulatory

4 Lack of recognised surrogates or correlates of efficacy

Absent recognised surrogates or correlates of efficacy, trials must be powered to show protection against disease. This means having to conduct larger, longer and more costly effectiveness trials.

5 Few regulatory authorities able to efficiently and flexibly regulate the primary licensure of a novel vaccine

The relative dearth of authorities able to license innovative vaccines efficiently means that developers are limited in their options and that they must choose between a more sophisticated NRA in a country where the need may be less, and an NRA lacking strong competencies, in both cases with delays in the process.

6 Lack of harmonisation on requirements across regulatory authorities in countries of use

The lack of adherence to international or regional standards means developers must often meet specific local requirements and potentially conduct bespoke clinical trials in specific jurisdictions irrespective of the clinical or epidemiological needs with higher costs and longer timelines.

Market & Policy

7 Insufficient public budgets for vaccine purchase and implementation of immunisation programmes

Pressure on health budgets or on the overall public finances may constrain governments' willingness to implement new immunisation programmes. This may leads developers to be reluctant to pursue "less popular" vaccines.

8 Lack of data for assessing potential impact of vaccination in particular specific target populations

In the absence of sound epidemiological data, developers are challenged to demonstrate the true impact of vaccination. Additionally investments to establish or strengthen epidemiology and surveillance capabilities may become necessary in order to increase the likelihood that vaccines will be adopted and implemented.

Manufacturing

9 Lack of ability to share production processes and/or facilities for multiple vaccines

Because vaccines utilise many different production technologies, facilities often require unique equipment. The fewer the opportunities to share production processes, the greater the time and costs developers must invest; this also increases the risk profile of those investments.

10 Long lead-time for establishing manufacturing capacity

Dedicated vaccine manufacturing lines or facilities require significant time to build. Unless decisions to start construction are taken at risk, waiting to invest in the manufacturing plant after initial clinical success is demonstrated can increase development time.

capable of conducting the required clinical development and regulatory processes. With only a few large vaccine developers possessing the financial means and strategic interest to license or acquire products from smaller development organisations, the current vaccine ecosystem is highly concentrated. This **limits the ability to develop partnerships** that leverage key stakeholder strengths to progress vaccines candidates through all stages of development to use in countries.

The regulatory challenges that impacted the time to market were concentrated in three areas. First, the fundamental deficiencies in knowledge or practices linked to the characteristics of the pathogens very often result in the **inability to identify or the lack of success in identifying relevant correlates of protection once a vaccine has successfully been developed**. This has a significant impact on the clinical trial design impacting their duration, size, and cost. Second, regulatory science is a niche field that requires not only scientific expertise and understanding but also specific experience in the process of reviewing regulatory submissions. Without such expertise, the regulatory reviews can be greatly delayed, with regulatory outcomes being conditioned by procedure. **Thus, the key expertise and experience are concentrated in a limited number of national regulatory authorities that can efficiently and flexibly regulate a vaccine in countries of origin.**[3] Third, there is **limited regulatory harmonisation** between countries, which creates inefficiencies and delays.

From a market and policy perspective, the main challenge identified was the constraint in a country's ability to purchase new vaccine products due to **limitations in public budgets and, more specifically, the limited resources dedicated to immunisation**. This factor, driven by the fact that vaccination is not always perceived as politically rewarding, makes vaccine demand uncertain, hence it is a source of risk for developers. Additionally, the willingness to fund vaccines from public budgets is increasingly dependent on **data and evidence, particularly for specific target populations**. If this data is absent, then additional efforts must be made to generate the data, which increases the cost and duration of vaccine development.

Finally, the work also identified a set of manufacturing challenges that directly impact the time to market of vaccines in development and their associated costs. First, the **need for the early establishment of new production lines for new vaccines** (i.e., drug substance, formulation, filling and finishing) generally resulting from the difficulty of sharing a large portion of the production processes and facilities, given the inherent uniqueness of each vaccine antigen. Second, the **limited availability of partners capable of receiving tech transfers** reduces the flexibility in the scale up of manufacturing capacity. Few companies are equipped with the appropriate technical know-how, equipment, and experience to be considered trustworthy partners from originators of the technology.

Efforts to address these challenges have been largely directed towards individual vaccine development rather than creating system-wide efficiencies that could decrease the required time and costs. The vaccine ecosystem research identified several areas where work was already underway or where specific interventions could be implemented to address those challenges.

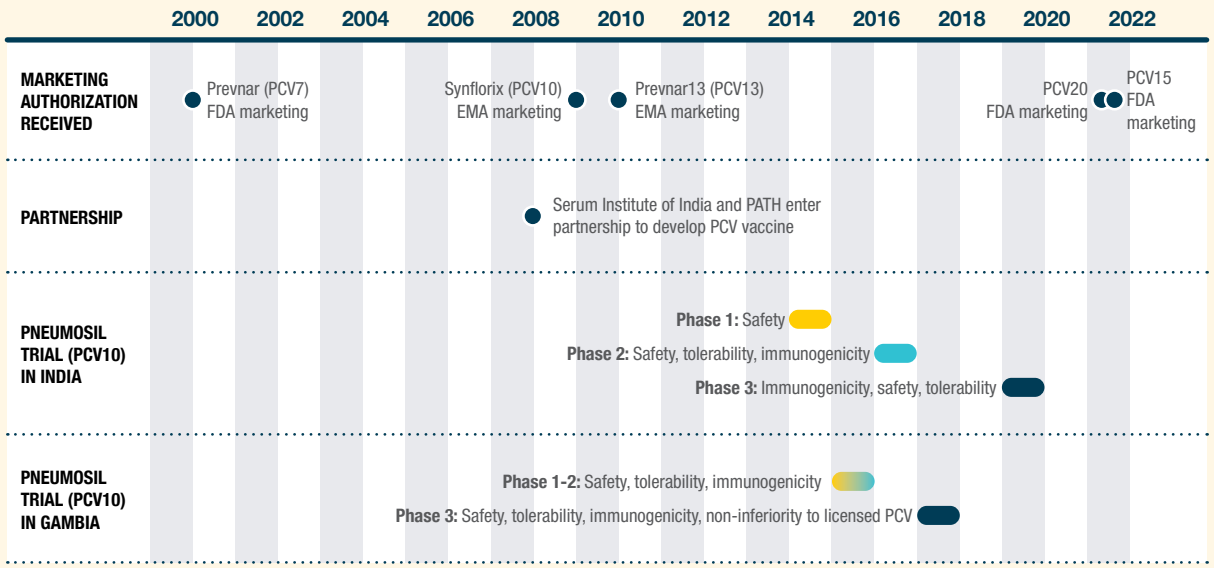
3. Country of origin is defined as the country where the initial dossier for authorisation of COVID-19 vaccines was filed.

The impact of the current vaccine ecosystem on clinical development timelines

Within the current vaccine ecosystem, an approximate duration of up to 10 years has been required for vaccines to progress through clinical development and marketing authorisation, particularly for vaccines to address endemic diseases. To better understand how COVID-19 vaccine development compares to such historical precedent, suitable comparator vaccines have been identified: pneumococcal conjugate vaccines (PCV), tuberculosis vaccines (TB), and H1N1 pandemic influenza vaccines (H1N1). The selection of those comparator vaccines was performed in collaboration with Wellcome Trust, based on similarities in global disease burden, target populations, financing and incentive mechanisms used to support their clinical development progression.

While both PCV and TB have high levels of burden of disease, the level of financial investment was of a different order of magnitude (< 1%) in comparison to COVID-19 vaccines.[14,15,16] Importantly, while PCV and TB provide interesting comparisons to COVID-19, each have different epidemiology, histories, and technical challenges, which may have impacted their vaccine development timelines. In addition, neither PCV nor TB are pandemic or outbreak-prone diseases. On the other hand, H1N1 vaccines were developed to meet the challenges of a pandemic and with the potential for a large global market that included high-income countries. H1N1 also had different implications for pharmaceutical companies' financial investment and returns compared to PCV and TB. The following sections detail the clinical development timelines of PCV, TB, and H1N1 vaccines, to highlight similarities and differences with COVID-19 vaccine development.

Figure 5: Development timelines for pneumococcal conjugate vaccines



Vaccines to prevent endemic diseases: a new vaccine for pneumococcal disease

The development of a new PCV, primarily aimed for use in low- and lower middle-income countries, is estimated to have begun in 2008, when a partnership between a vaccine manufacturer and PATH was put in place. Clinical trials for the vaccine candidate began in 2014, and the vaccine received marketing authorisation from national regulators in 2020.[17] This vaccine development experience illustrates a "fast" timeline of approximately seven years to complete all required clinical development phases and receive marketing authorisation. It should be noted that this specific PCV vaccine development significantly benefited from prior work on pneumococcal polysaccharide and conjugate vaccines (e.g., standard assays and correlates of protection were already established, etc.) and conjugation technologies. Furthermore, the disease burden is concentrated in younger children (< 5 years of age), there is an existing market and financing via the advance market commitment from Gavi, the Vaccine Alliance, and the disease is distributed across all geographies with high global burden causing an estimated 1.3 million deaths and 52 million disability-adjusted life years (DALYs) in 2019.[18] The combination of these factors may have contributed to the accelerated timelines for development and marketing authorisation. Figure 5 provides an overview of the clinical development timelines for several marketed PCVs.

Vaccines to prevent endemic diseases: a vaccine for tuberculosis

While tuberculosis has a similar disease burden to SARS-CoV-2, the disease is concentrated in low- and middle-income countries, with more prevalence in the older populations.[19, 20] TB caused an estimated 1.4 million global deaths annually and over 66 million DALYs in 2019.[21] Further, TB vaccines face a specific set of technical development challenges that did not impact SARS-CoV-2. For example, TB is a chronic infection, and to date, there are limited numbers of vaccines targeting chronic infections; TB is slow to grow in animals and difficult to cultivate in vitro; and there are limited in vitro assays to assess immunity. All of these factors may contribute to longer vaccine development timelines and a higher failure rate. Currently, there are three promising TB vaccine candidates in development, but these candidates will require an estimated minimum of 15 to 20 years before their market authorisation.[19, 20]

Figure 6 provides an overview of the clinical development timelines for three TB candidate vaccines.

Figure 6: Development timelines for TB candidate vaccines

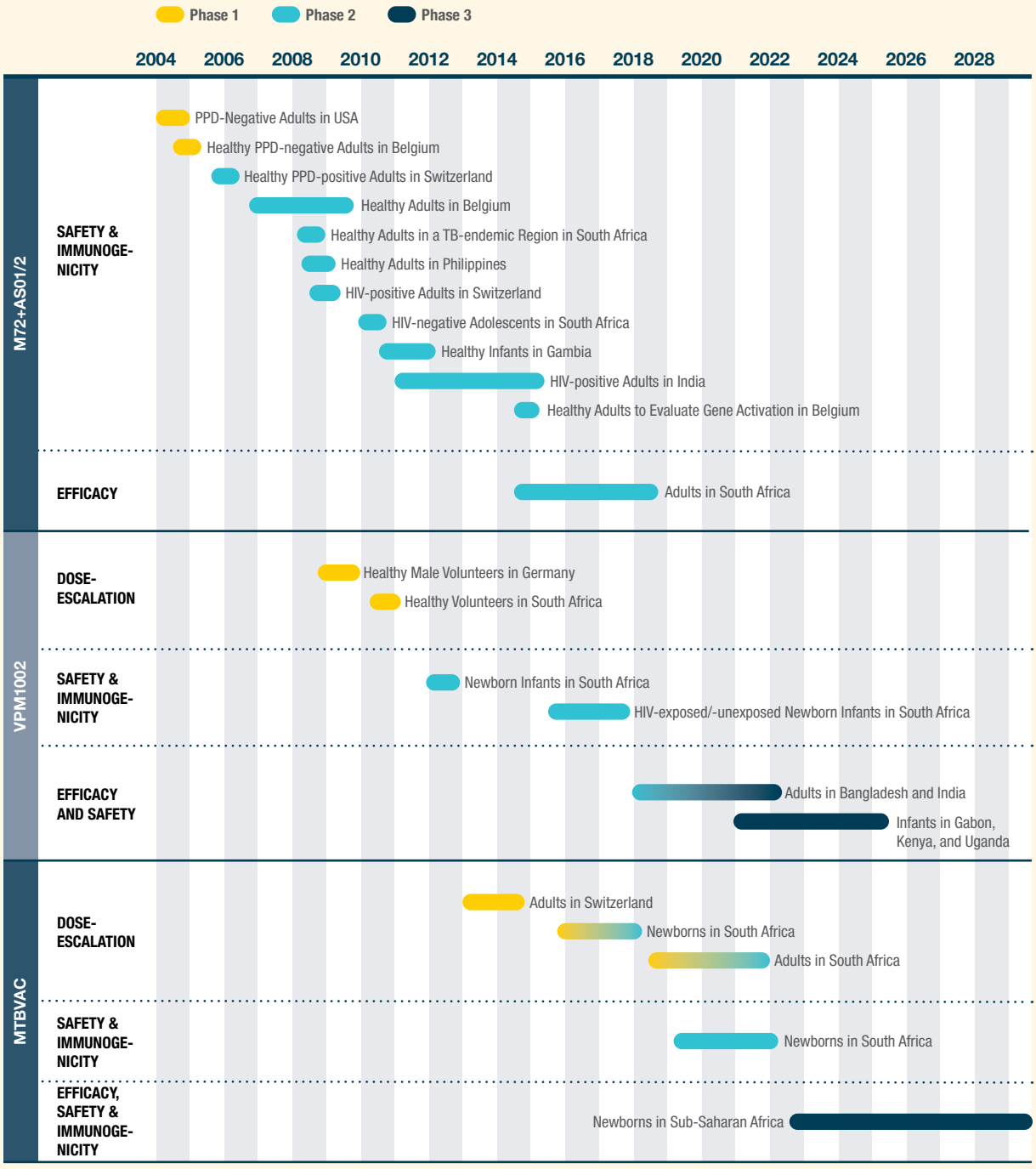
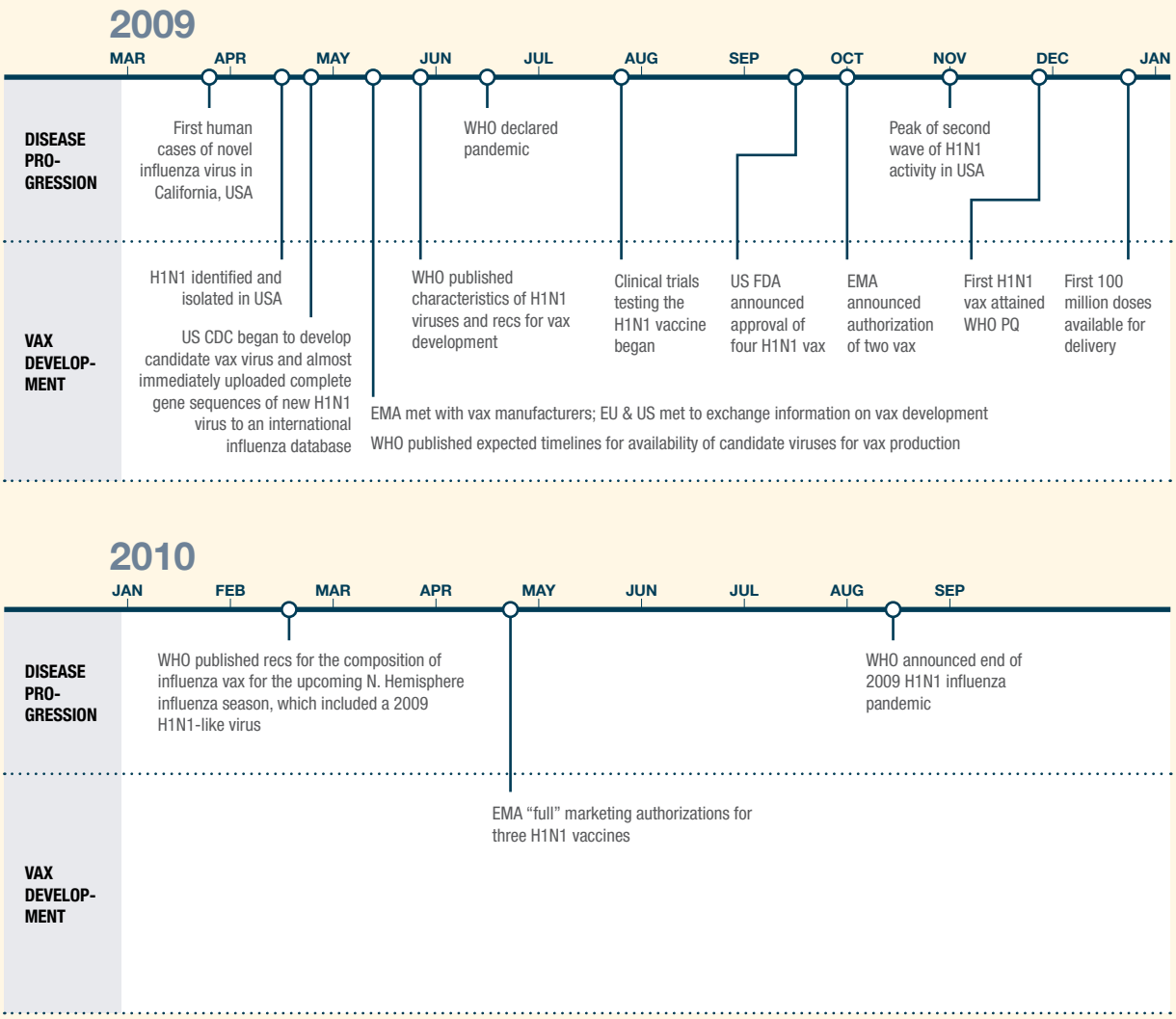


Figure 7: Overview of timelines of H1N1 disease progression and vaccine development timelines



Vaccines to prevent pandemic disease: a vaccine for H1N1 pandemic influenza

In assessing a closer parallel to COVID-19, H1N1 was also a pandemic vaccine that leveraged existing vaccine research whose development and authorisation was achieved 153 days after detection of the first H1N1 case.[22] There were an estimated 151,000-575,000 deaths from H1N1 virus infection during the pandemic's first year.[22] The development of the new H1N1 vaccine was a strain change on an existing product that underwent an annual adjustment process to incorporate a new influenza strain, which allowed simpler vaccine research and development processes. Further, the H1N1 vaccine leveraged the significant level of regulatory planning conducted in advance (e.g., the use of a specific type of marketing authorisation to allow a vaccine to be developed and authorised but not marketed before an influenza pandemic, availability of assays, established WHO pre-qualification process, regulator collaboration) to support rapid access to influenza vaccines in the event of an epidemic.[23] Together, these elements helped to enable rapid vaccine development following the detection of the first H1N1 case, with H1N1 vaccines receiving regulatory approval 153 days later.

Figure 7 provides an overview of the H1N1 disease progression and vaccine development timelines.

While H1N1 vaccines were developed at a record-breaking pace, there were critical challenges that served as key lessons learned and ultimately contributed to the accelerated COVID-19 development timelines. First, the limitations of mass-producing egg-based vaccines contributed to interest and investment in new technologies that could be quickly scaled up in a pandemic situation.[24,25] Second, as adjuvants were anticipated to play a critical role for H1N1 vaccines, given their ability to induce a sufficient immune response and their potential dose-sparing properties to meet the potential demand, the H1N1 pandemic shone a light on the need to progress on adjuvant research given the associated adverse events, which resulted in a revision of recommendations by the European Medicines Agency.[26, 27]

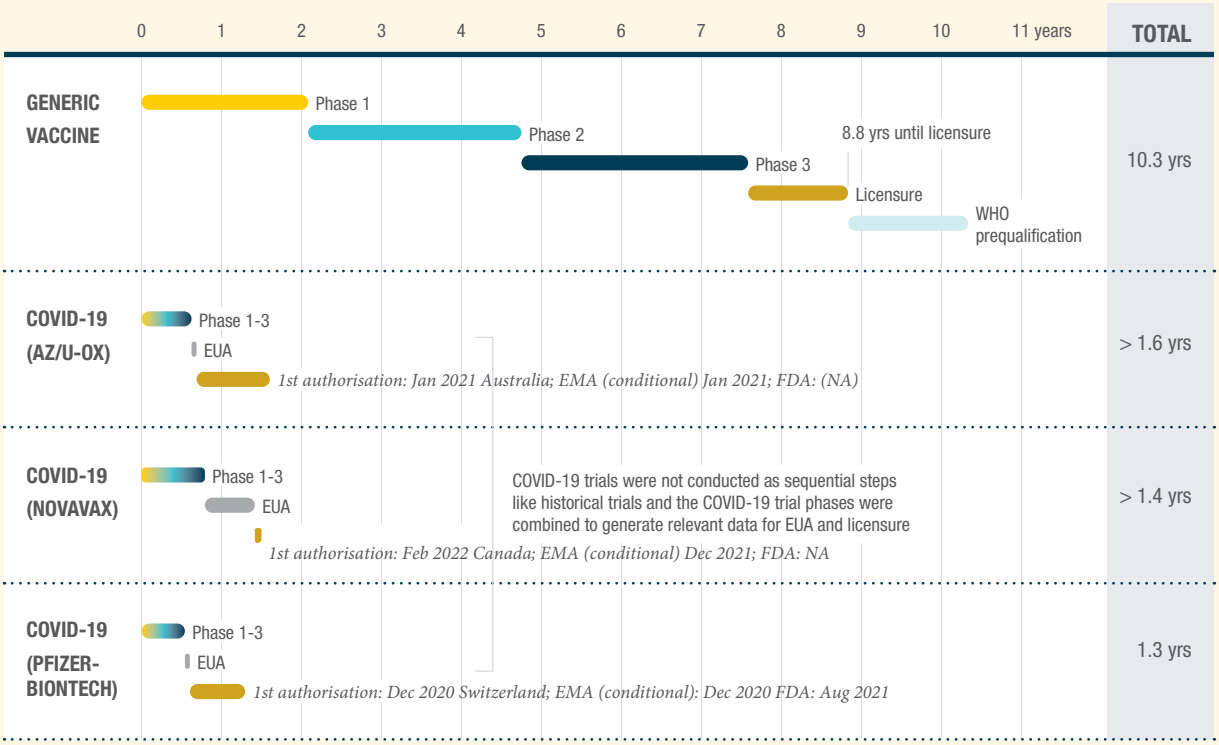
COVID-19 vaccines

Until the SARS-CoV-2 pandemic, all key stakeholders generally accepted the extended vaccine development and regulatory process timelines and the low success rates of vaccine candidates. Within the 24 months, since SARS-CoV-2 was first identified in late December 2019, 28 vaccines have been developed and approved by at least one country using several different technologies, including mRNA, viral vector, inactivated, and protein subunit. The rapid development of COVID-19 vaccines and the breadth of platform technologies being used represents a paradigm shift in how the global immunisation community can approach the future development and approval of vaccines, and it raises the need to identify the factors that could be replicable, particularly for vaccines targeting emerging epidemic pathogens and endemic diseases.

Figure 8 details a comparison of development and licensure timelines of three COVID-19 vaccines, each using different platform technologies (i.e., mRNA, non-replicating viral vector, and protein subunit), to the historical development of a generic vaccine.[1-5]

In conclusion, the analysis on the vaccine comparators shows a stark contrast between the historical vaccine development and regulatory approval timelines and financial investment compared to the COVID-19 vaccine. This analysis highlights the importance of understanding what factors contributed to this rapid pace of development and how, if possible, the factors could be replicated for future vaccine development.

Figure 8: Comparison of historical and COVID-19 vaccine development and authorisation timelines



Assumptions:

1. Estimates for each clinical trial phase include time required for activities necessary to transition to next trial phase including data analyses, protocol development, regulatory requirements, manufacturing scale-up, decision-making
2. The time estimates for each phase are dependent, among the other factors, on disease incidence in trial sites which impacts recruitment and case acrual, particularly for Phase 3 trials
3. Time requirements for Phase 3 trials are based on the workload required to generate vaccine efficacy data (i.e., time requirements for immunogenicity or non-inferiority trials are generally significantly shorter)

The enabling factors that accelerated the development and approval of COVID-19 vaccines

Factors identified through the literature and consultations

Through a rapid literature appraisal, interviews, and a survey, a total of 32 factors contributing to the rapid development and authorisation of COVID-19 vaccines were identified. A regression analysis was used to quantitatively highlight how the factors may have interacted with each other and provide robustness to identified factors. See Annexes 1 and 2 for more information regarding the methodology and results utilised.

Using these data sources and an evidence matrix, a level of confidence was assigned to each factor to indicate its perceived contribution to the accelerated timelines for COVID-19 development and authorisation. The approach is described in detail in Annexe 2. Checkmarks per data source were given if there was consensus that the factor played a role in accelerating timelines; if not, then the factor was assigned "mixed". The evidence from the three data sources was then interpreted as the level of confidence that the factor played a role in accelerating the development and authorisation timelines. The possible levels of confidence were "high", "medium", "low" or "very low". They were based on the number of sources and whether the data sources reached the same or similar conclusions regarding the factor impact. **It should be noted that if a factor received a low or very low rating, this does not mean that it did not play a role in impacting the timelines but that the literature or consultations did not consistently recognise the evidence on whether this factor played a role**.

This section provides an overview of the identified factors and their perceived impact on timelines. Note that the factors are not listed in any order of priority.

The identified factors and their respective confidence levels are detailed in Figure 9.

The 32 factors are outlined in detail below per the four areas in which the research was structured. The approach to identify factors is further described in Annex 1 and 2.

The pandemic context

The analysis identified 10 factors related to the nature and impact of the SARS-CoV-2 pandemic, which led to significant health, economic, and social impacts ultimately leading to high political will. These factors are important as they serve to provide the context in which vaccine development and authorisation activities were being conducted. Based on our analysis, these factors were not often documented in published or unpublished literature, but likely played an important role in influencing stakeholder behaviours. A description of the factors is below.

- **There were significant health, economic, and social impacts worldwide**: SARS-CoV-2 created significant disruption to the "way of life" and ability to work across the globe, including in high-income countries. By the end of 2020, there were over 1.8 million reported deaths and an estimated excess mortality of at least 3 million persons.[8] The International Monetary Fund projected that the global economy would contract by -3%, which was worse than the 2008-09 financial crisis, and it flagged the high risk for even more severe economic outcomes.[10] During this time, many countries were already in lockdown, which heavily impacted daily life, potentially increasing inequities within countries as well as having other potential impacts related to mental health and domestic violence.[11,12] This factor was consistently identified in the literature as well as in the consultations with experts, thus it is rated with a high level of confidence as having an impact on the timelines for COVID-19 vaccine development.
- **The high impact of SARS-CoV-2 changed the usual risk-benefit balance for vaccine development and authorisation:** This resulted in changes of standard behaviours and the prioritisation of human and financing resourcing towards vaccine development.
- **Decision-making was rapid, with at-risk decisions taken earlier in the process:** The high impact of SARS-CoV-2 resulted in high demand from the world, and it encouraged more rapid and earlier decision-making compared to standard vaccine development (e.g., decisions to scale-up manufacturing were taken at an early stage).
- **The use of partnerships (e.g., academic with industry, etc.) allowed the ability to leverage strengths to develop vaccines and obtain regulatory authorisation:** The number of

Figure 9: Overview of the identified factors and level of confidence assessment

✓ Feedback on the factor was the same or similar Mixed: Feedback on the factor was not aligned

High Moderate Low Very low

	Factor description	Literature	Interviews	Survey	Confidence
Pandemic context	Significant health, economic, and social impacts worldwide, including high impact in high income countries	✓	✓	✓	High
	The high impact of SARS-CoV-2 changed the usual risk-benefit balances, increasing the risk appetite of all key stakeholders		✓	✓	Moderate
	Decision making was rapid with at-risk decisions taken earlier in the process		✓		Low
	The use of partnerships (e.g., academic with industry, etc) allowed the ability to leverage strengths to develop vaccines and get regulatory approvals		✓		Low
	There were high levels of trust between all key stakeholders, but particularly between manufacturers and regulators; manufacturers and clinical development partners		✓	✓	Moderate
	There were high levels of political will and leadership		✓	✓	Moderate
	Pandemic preparedness, including pre-defined processes /structures were in place as well as existing organisations with pandemic/epidemic mandates		✓		Low
	Researchers were more open to sharing preliminary findings and information	✓	✓	Mixed	Moderate
	The initial age distribution of the burden of disease for SARS-CoV-2 was on older, adult populations			✓	Very low
	High levels of expertise were devoted to COVID-19 vaccine research and development and authorisation (e.g., all resources were allocated to COVID-19 vaccine research and development)		✓		Low
Financial factors	The potential for a market, which targets the world's population that may require repeated vaccination	✓	Mixed	Mixed	Moderate
	Unprecedented demand for COVID-19 vaccine generated by the high SARS-CoV-2 burden and there were no other pharmaceutical interventions were available	✓	✓	✓	High
	Unprecedented financial investments from multiple funding sources were made in the research and clinical development of COVID-19 vaccines	✓	Mixed	✓	Moderate
	There were materially large advance purchase agreements made with countries prior to the completion of clinical trials	✓	Mixed	✓	Moderate
	The pooling and/or coordination of financial resources created an attractive global market	✓	Mixed	✓	Moderate

✓ Feedback on the factor was the same or similar Mixed: Feedback on the factor was not aligned

High Moderate Low Very low

	Factor description	Literature	Interviews	Survey	Confidence
Clinical development factors	Clinical trials were designed with collapsed/consolidated phases and / or multiple steps were conducted in parallel	✓	✓	✓	High
	There was a high SARS-CoV-2 transmission rates in the clinical trial sites	✓		✓	Moderate
	Trial sponsors and stakeholders conducted additional activities to ensure high participant enrolment	✓	✓	Mixed	Moderate
	There was more use of innovative statistical approaches (e.g., Bayesian approaches to measure endpoints)	✓	Mixed	Mixed	Very low
	There was strong and flexible research capacity and clinical trial infrastructure in the areas with high burden of disease	✓	✓	✓	High
	There were decades of prior research on the vaccine platforms	✓	✓	✓	High
	There was pre-existing vaccine research on SARS-CoV-1 and MERS as well as other diseases	✓	✓	✓	High
	SARS-CoV-1 and MERS were previously studied extensively in animal models	✓	Mixed	✓	Moderate
Regulatory factors	Study requirements and non-clinical standards (e.g., pharmacology, toxicology) were pre-defined, communicated, and used	✓		Mixed	Very low
	Regulatory authorities aligned data requirements to those essential for emergency approval for clinical trials and for manufacturing	✓	✓	✓	High
	Regulatory authorities provided flexibility on the sequencing of steps to assess safety, immunogenicity, and efficacy	✓	✓		High
	Regulatory authorities adopted accelerated review processes and prioritized their reviews, including rolling reviews	✓	✓	✓	High
	Regulatory authorities maintained a high focus on safety, but accepted uncertainty on other aspects	✓	✓	✓	High
	Emergency use authorisation or conditional approvals were used to ensure rapid availability of vaccines	✓	✓	✓	High
	Regulatory harmonization and reliance were appropriately used by regulatory authorities in countries of use		✓	✓	Moderate
	Forums or working groups provided for open and transparent discussion on regulatory topics		✓		Very low
	There were high levels of collaboration, discussion, and access between regulatory authorities in producing countries and clinical trial sponsors	✓	✓	✓	High

potential players interested in and available to engage in vaccine development increased. This resulted in new partnerships that leveraged the expertise and experience of stakeholders for both vaccine research and development and regulatory processes.

- **There were high levels of trust between all stakeholders, especially between vaccine manufacturers and regulators or clinical development partners:** The processes from pre-clinical to regulatory reviews benefited from the existing relationships of the key stakeholder engaged. This level of trust helped to accelerate the timelines, particularly for the initial authorisation of vaccines.
- **There were high levels of political will and leadership:** The high visibility and uncertainty of SARS-CoV-2 generated a high level of political will and leadership, which placed emphasis and prioritised COVID-19 vaccine development and authorisation.
- **Pandemic preparedness, including pre-defined processes/structures, were in place as well as existing organisations with pandemic/epidemic mandates:** The use of previously defined processes for pandemic preparedness was leveraged. For example, the Global Influenza Surveillance and Response System was used to source and type COVID-19 samples, and first authorisation generally followed the emergency use authorisation processes that had already been developed. Further, the availability of organisations, such as CEPI and BARDA, to respond to the pandemic was important to make the initial at-risk investments in vaccine development.
- **Researchers were more open to sharing preliminary findings and information:** The immediate sharing of genomic sequence informed vaccine design and accelerated timelines.
- The initial age distribution of the burden of disease for SARS-CoV-2 was on older, adult populations: This may have contributed to the risk-benefit of key stakeholders, whereas if the burden had been immediately concentrated in children there may have been less risk-benefit, ultimately impacting timelines.
- **High levels of expertise were devoted to COVID-19 vaccine research and development and authorisation (e.g., all resources were allocated to COVID-19 vaccine research and development):** There was a high sense of urgency from all stakeholders, resulting in all available resources being reallocated to COVID-19 vaccine research and development and authorisation processes. Note that this came with a negative consequence that delayed and even halted the research and development and authorisation of vaccines targeting other diseases.

Unprecedented financial investment

Five factors related to the financial investments were identified from all three data sources. Although the factors were identified from all data sources, the feedback on their impact on the acceleration of COVID-19 timelines was mixed, particularly for the interviews, indicating that the financial investments likely had a more complex impact on the timelines.

- **The potential for a market that targets the world's population that may require repeated vaccination:** This resulted in unprecedented and potentially long-term revenues that may have influenced additional players' interest to enter the vaccine development space.
- **Unprecedented demand for COVID-19 vaccines generated by the high SARS-CoV-2 burden:** There were no other preventive pharmaceutical interventions available at the time of COVID-19 vaccine development. Political decision makers view vaccines as a key preventive intervention that could eliminate the large health, societal, and economic impacts and restore the way of life. This factor was the only financial factor that all data sources agreed on as having an impact on the timelines.
- **Unprecedented financial investments from multiple funding sources were made in the research and clinical development of COVID-19 vaccines:** Multiple vaccine candidates received substantial push investment to support the entire development process, which removed the standard assessment periods and barriers to advance vaccine candidates. Ultimately this accelerated decision-making among vaccine developers or manufacturers due to the availability of immediate funding or the guarantee to recoup their investment costs.
- **Materially large advance purchase agreements were made with countries prior to the completion of clinical trials:** Vaccine developers and manufacturers received significant pull funding (i.e., incentives for late-stage development and advance purchase agreements), which increased the risk appetite of manufacturers due to the increased likelihood of future demand materialising. This also helped to create a large and financially attractive market.
- **The pooling and/or coordination of financial resources created an attractive global market:**

It created additional guarantees for a vaccine market that de-risked the decision-making on vaccine candidates and removed financial constraints/limitations on whether to advance vaccine candidates.

Proactive regulatory approach

This analysis identified eight factors specifically related to the proactive regulatory approach for COVID-19 vaccines. The majority of these factors were identified in both the literature and the consultations, with many of these factors receiving a high level of confidence of their perceived impact in the development and authorisation timelines. Further, the majority of the regulatory factors were rated above the median based on the survey results, and all 46 interviewee respondents also identified these factors. The high level of consensus from the consultations indicates that the regulatory factors played a key role in accelerating timelines. See below for a detailed description.

- **Study requirements and non-clinical standards (e.g., toxicology) were pre-defined, communicated, and used:** Removed ambiguity for all stakeholders on the key data needs and requirements, allowed for easy alignment between the key stakeholders.
- **Regulatory authorities limited data requirements to those essential for emergency approval for clinical trials and for manufacturing:** Regulatory authorities adopted a platform review approach, accepted pre-existing animal model data, and only required full validation of production methods and assays for Phase III for vaccine developers that had pre-existing data from other vaccine development programmes using the same platform technology. Further, regulatory authorities provided flexibility on the timing of when certain data should be provided (e.g., the developmental-reproductive toxicology studies for repeated dosing, approval of vaccines containing genetically modified organisms, etc.).
- **Regulatory authorities were flexible regarding the sequencing of clinical evaluation steps to assess safety, immunogenicity, and efficacy, including the merging of clinical phases:** The prioritisation of certain application steps and the use of overlapping steps led to much faster process with a clear prioritisation of the safety and efficacy data.
- **Regulatory authorities prioritised their reviews, including rolling reviews:** Clear prioritisation by regulatory authorities allowed for immediate review and fast processing, as well as the overlapping of certain process steps (e.g., rolling reviews, shortened, or overlapping processing and submission timelines, immediate review of trial data).
- **Regulatory authorities maintained a high focus on safety but accepted uncertainty on other aspects:** Regulatory authorities enabled the progression of clinical development on the basis of available short-term data, and they allowed the continued collection and provision of long-term data as part of manufacturers' commitments.
- **Emergency use authorisation or conditional approvals were used to ensure rapid availability of vaccines:** Allowed for immediate use of the vaccine once it received emergency or conditional authorisation. Note that many countries that did not have these processes in place took the opportunity to establish these processes or to pass emergency legislation.
- **Regulatory harmonisation and reliance were appropriately used by regulatory authorities in countries of use:** The use of regulatory harmonisation (i.e., alignment of regulatory requirements between countries) and reliance simplified the vaccine authorisation for many countries of use, ultimately reducing timelines by streamlining data requirements and review processes. A strong example of a successful regulatory reliance mechanism is WHO's Emergency Use Listing supported by different regulatory bodies in countries of use to rapidly assess the acceptability of COVID-19 vaccines. It is also important to note there remains a high need for the transparent sharing of data and information to countries of use so that they can make evidence-based decisions.

- **Forums or working groups provided for open and transparent discussion on regulatory topics:** Allowed regulators to learn from each other and to transparently discuss any issues or approaches to reviewing data. This likely impacted subsequent authorisation of vaccines and may have contributed to public trust and confidence in COVID-19 vaccines.
- **There were higher levels of collaboration, discussion, and access between regulatory authorities in producing countries and clinical trial sponsors:** Immediate and early collaboration between regulatory authorities and clinical trial sponsors allowed for a baseline understanding of potential challenges and any ongoing revisions during the clinical trial phases to ensure expectations were being met.

Faster clinical development

Eight factors were identified related to the clinical development strategies and practices applied for COVID-19 vaccines. These factors impacted not only the vaccine design, but also the design of pre-clinical and clinical activities. Many of the factors were recognised across all three data sources, with the scientific advancements in vaccine platforms, previous research on coronaviruses, and strong clinical development infrastructure receiving high levels of confidence for their perceived impact on the acceleration of COVID-19 vaccine development timelines.

- **There were decades of prior research on the vaccine platforms:** Prior work was conducted on SARS-CoV-1 and MERS on DNA, subunit, and viral vector platforms, which were all leveraged for COVID-19 vaccines.
- **There was pre-existing vaccine research on SARS-CoV-1 and MERS as well as other diseases:** There was substantial evidence available regarding the immunogenicity of coronavirus S-protein vaccine target. Further, the full-length genome phylogenetic analysis suggested that the genomic sequence of SARS-CoV-2 is almost 78–80% similar to that of SARS-CoV-1. Both SARS-CoV-1 and SARS-CoV-2 bind to the same host cell receptors.
- **SARS-CoV-1 and MERS were previously studied extensively in animal models:** There was also pre-existing research on animal models, reducing the need for animal research on SARS-CoV-2 and enabling COVID-19 vaccine candidates to progress rapidly through pre-clinical research phases.
- **Clinical trials were designed with collapsed/consolidated phases and/or multiple steps were conducted in parallel:** The use of collapsed or consolidated phases allowed for the rapid determination of safety and efficacy endpoints as well as accelerating decision-making during clinical trial phases.
- **There was a high SARS-CoV-2 transmission rate in the clinical trial sites:** There was a rapid accrual of SARS-CoV-2 cases in the trial sites that allowed the trials to quickly reach their safety and efficacy endpoints with adequate statistical power. Further, there was high enrolment with participants of diverse backgrounds, including some risk groups, and the trials produced more generalisable data faster.
- **Trial sponsors and stakeholders conducted additional activities to ensure high participant enrolment:** Additional community engagement and educational campaigns were carried out to ensure high participant enrolment in clinical trials. This resulted in trials > 1,000 participants and influenced the ability to quickly reach clinical trial endpoints (e.g., more community outreach, etc.).
- **There was more use of innovative statistical approaches (e.g., Bayesian approaches to measure endpoints):** The trials produced more generalisable data with credible confidence intervals for efficacy that was easier to interpret and assess.
- **There was strong and flexible research capacity and clinical trial infrastructure in the areas with high burden of disease:** There was a faster trial set-up and implementation due to available capacity and expertise and strong infrastructure in areas with high disease burden.

Assessment of the interactions between the identified factors

While the identified factors all independently impacted the development and authorisation timelines of COVID-19 vaccines, the factors also interacted with each other to change the risk-benefit assessment of key stakeholders involved in vaccine research, development, and authorisation. This section further describes the interaction of the factors with each other.

Figure 10 provides an overview of the four areas and how they interacted to accelerate the timelines for COVID-19 vaccine development and approval.

The pandemic context – the significant health, economic, and social impacts leading to high levels of political will

Of the 10 factors related to the nature and impact of the SARS-CoV-2 pandemic, the most consistently identified factor was the **significant health, economic, and social impacts** experienced worldwide, including in high-income countries. This factor drove the behaviours and actions of all key stakeholders and likely created additional factors that had a significant impact on the accelerated timelines.

The significant health, economic, and social impacts resulted in **high levels of political will and a sense of urgency**, which likely led to **high levels of financial investments and to high prioritisation of human resources** towards the development and authorisation of COVID-19 vaccines. Interviews also highlighted that there was a change in risk-benefit assessment among key vaccine development and regulatory stakeholders, likely driven by the impact of the SARS-CoV-2 pandemic and, in the case of clinical development stakeholders, the availability of financial investments to support a rapid response. The change in risk-benefit assessment was a key factor that impacted the behaviour of all stakeholders and is seen across all the topic areas. Further, there was **more rapid decision-making** during the clinical development and a more p**roactive approach for the regulatory reviews**. Another important factor related to the context of the pandemic is that it provided **more opportunities for partnerships**. This encouraged collaboration among all key stakeholders (e.g., government, academia, and biotechnology and pharmaceutical companies), as well as new organisations entering the vaccine development space. These partnerships allowed the stakeholders to combine their strengths, experiences, and relationships, which ultimately accelerated the timelines. This factor was also found to be statistically significant in the regression analysis. Finally, scientific researchers' willingness to **share research outputs** was identified as an important factor in facilitating rapid access to important information relevant to vaccine design, particularly regarding the SARS-CoV-2 pathogen and the evolving epidemiology of COVID-19.

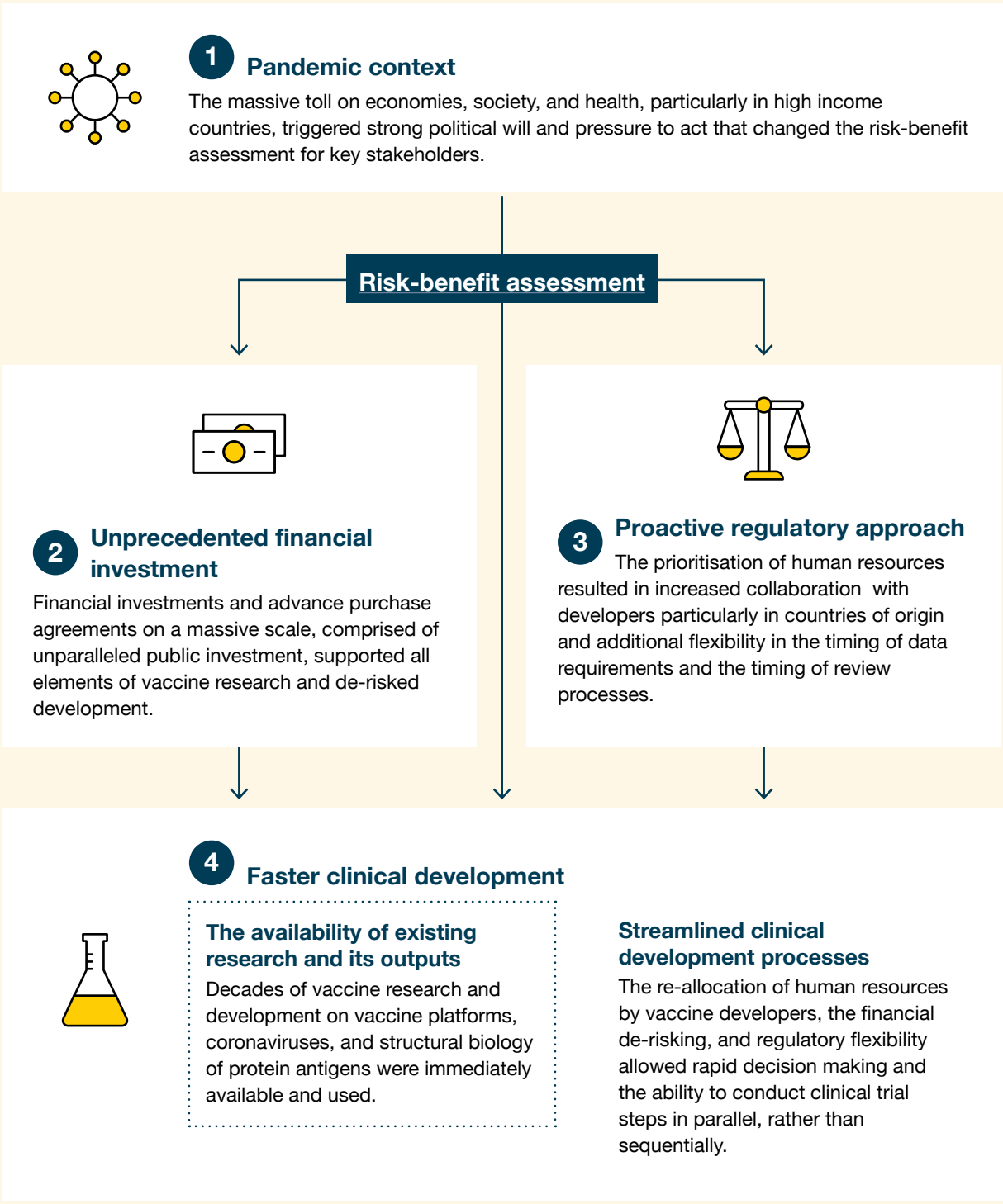
The factors linked to the nature and impact of the SARS-CoV-2 pandemic highlight the underlying context in which COVID-19 vaccines were being developed, and its importance in influencing the actions and behaviours of key stakeholders throughout the vaccine development and authorisation process.

Unprecedented financial investment – contributed to more efficient decision-making

The **unprecedented size of financial investments from multiple sources** made towards COVID-19 vaccine clinical development and the **advance purchase agreements** between governments and pharmaceutical companies were identified as two key factors that impacted the timelines. Together, both factors helped to **de-risk clinical development and to make resource-allocation decisions** that vaccine developers generally face, which enabled **faster decision-making** and a **more efficient clinical development process**. This in turn enabled candidate COVID-19 vaccine candidates to progress more quickly through the clinical development process compared to a non-pandemic context.

The **unprecedented level of demand for COVID-19 vaccines** to address the SARS-CoV-2 disease burden in the absence of other pharmaceutical interventions was the third key financial factor identified. The demand for COVID-19 vaccines, with a total addressable **market of the entire global population**, served as a critical commercial incentive

Figure 10: Interaction and impact of key factors on COVID-19 vaccine development and approval timelines



for vaccine developers to rapidly develop COVID-19 vaccines for use.

Finally, this level of demand led to the **pooling and coordination of funding** to support both COVID-19 vaccine development and create an attractive global market for approved vaccines. Linked to this factor, the consultations revealed that the early financing provided by organisations focused on emergencies, such as CEPI and BARDA, played a role in accelerating timelines for clinical development. All the financial factors helped de-risk COVID-19 vaccine development largely by **cutting out the standard assessment periods** that occur after every clinical trial phase and **allowing for clinical research and development activities to be conducted in parallel** rather than sequentially.

These five factors combined demonstrate the important role those financial investments and incentives played in accelerating COVID-19 vaccines, particularly by creating viable commercial incentives and de-risking the clinical development process for vaccine developers.

Proactive regulatory approach – prioritisation of human resources and increased collaborations

From the outset, regulatory authorities in countries of origin articulated the key data requirements that would enable **emergency use authorisation**, which helped to support rapid access to vaccines shown to be effective in clinical trials. On this basis, regulators **advised vaccine developers about the minimum clinical, non-clinical, and manufacturing data required** to support the regulatory reviews and approvals of candidate vaccines. Thus, clinical trial protocols were able to be designed to generate the necessary evidence required. As is the case for traditional vaccine development, the safety and efficacy of candidate vaccines were still the two highest priorities for regulators in countries of origin when assessing vaccines for emergency use. While aligning on the requirements was important, consultations also highlighted that the **immediate and ongoing collaboration with regulators** was instrumental in improving timelines.

Linked to the above, as emergency or conditional authorisation pathways were employed, regulators accepted a level of uncertainty about other vaccine product characteristics compared to regulatory reviews performed for full market authorisation of non-pandemic vaccines. This **prioritisation of the most important characteristics and acceptance of unknowns on less important characteristics** (e.g., duration of protection) again highlights the pandemic context and how it influenced behaviours to change the standard vaccine development and approval timelines.

In addition to the upfront decisions that regulatory authorities made to define the data required to support emergency authorisation, there were also several critical process-related actions that regulators in countries of origin took. First, **regulators performed accelerated reviews of COVID-19 vaccine dossiers, prioritising COVID-19 reviews over other non-SARS-CoV-2 related health products**, which reduced standard review times. In many cases, the COVID-19 reviews were conducted in approximately 1 to 2 weeks because all human resources were prioritised towards these reviews. Whereas in normal circumstances, the regulatory review can last anywhere from 3 to 12 months given the competing priorities. Further, regulators also allowed for **flexibility in the sequencing of submission and review** of safety, immunogenicity, and efficacy assessments, and they **conducted rolling reviews** of new data and information as they became available from clinical trial sponsors. In a non-pandemic context, regulators generally review dossiers only once all information and data have been submitted. While many praised regulators' level of collaboration and prioritisation, this may not be fully replicable in a non-pandemic environment due to the need to spread regulatory resources, expertise, and experience across a range of health topics. Further, it is important to note that regulators' prioritisation of COVID-19 interventions had a negative impact on pharmaceutical interventions of other diseases during the pandemic and put significant pressure on staff workload and morale.

The findings from this research indicate that the regulatory review and process for first authorisation was done in an efficient manner largely due to the level of experience and expertise of the stringent regulatory authorities. However, the regulatory review and process by countries of use faced more challenges. First, many countries did not have emergency use authorisation processes in place but have taken this opportunity to develop these processes. Second, while **regulatory harmonisation**

and reliance[4] was used and resulted in some efficient authorisations in countries of use, consultations found there is a need to continue to improve harmonisation and reliance mechanisms. One potential factor that positively impacted the regulatory review and process in countries of use was the **use of inclusive forums for open, transparent discussions**, under the Chatham House rule. One such example was a Regulatory Advisory Group, which is co-led by WHO and CEPI and consists of members from 13 countries and regulatory authorities. It was established to provide feedback on regulatory science questions of an agnostic nature to support and promote ongoing regulatory development among COVID-19 vaccine developers, and to act as a forum to discuss key regulatory development issues. These forums were cited by many as being important as they provided opportunities for the regulators to learn from each other, likely expediting the subsequent regulatory reviews and leading to quicker access to COVID-19 vaccines in more countries.

Faster clinical development – the availability of existing research and outputs and streamlined COVID-19 vaccine clinical development processes

Nine factors were identified related to clinical development advancements and practices. These factors could be divided into two subgroups: (i) the scientific advancements made in vaccine research and development that were not specifically related to the SARS-CoV-2 pandemic, and (ii) streamlined clinical development processes for COVID-19 vaccines.

Two factors falling into the first subgroup include the **decades of prior research performed to develop new vaccine platform technologies** (e.g., mRNA and non-replicating viral vectors), and the **prior research and development activities on coronaviruses with pandemic or epidemic potential** (e.g., SARS-CoV-1 and MERS). The technology of new vaccine platforms was essentially at a stage where it could be immediately leveraged for COVID-19 vaccine development, which supported the rapid design of vaccine candidates for pre-clinical and clinical testing. Further, prior research and vaccine development activities due to the SARS-CoV-1 and MERS outbreaks, including early-stage clinical testing, armed the vaccine developers with a strong understanding of the SARS-CoV-2 structural biology, mode of transmission, and areas of the virus to target for a strong immune response (e.g., the spike protein). Once vaccine candidates had been designed for testing, vaccine developers were able to leverage prior findings from animal model testing of SARS-CoV-1 and MERS vaccines, and they rapidly identified potential animal models that would be suitable for the evaluation of COVID-19 vaccines. In summary, the prior research on the optimal immunogenic targets for coronavirus vaccines and the readiness of new vaccine platform technologies enabled COVID-19 vaccine candidates to be designed for pre-clinical and subsequent clinical testing more quickly than the historical precedent.

The second subgroup of factors relates to a more streamlined process towards clinical development. The scale of financial investments helped to remove the usual financial barriers and **accelerate decision-making related to clinical trials. It also allowed clinical trial steps to be conducted in parallel.** Further, when vaccine candidates were ready for human testing in Phase I/II/III trials, the clinical trials were designed with **consolidated phases and multiple steps in the trials were conducted in parallel**, which allowed for the rapid progression of candidates through the required clinical development phases. Additionally, many of these trials were conducted in areas that had both **strong and flexible research capacity and clinical trial infrastructure and high burden of SARS-CoV-2**. These factors also contributed to the accelerated timelines.

These factors helped to facilitate the rapid design of COVID-19 vaccine development programmes and the execution of high-quality clinical trials for first generation COVID-19 vaccine candidates, **quickly reaching the required enrolment and number of events needed** for powered measurement of key trial endpoints that regulatory authorities could review for emergency use authorisation.

4. Regulatory reliance refers to the act whereby the regulatory authority in one jurisdiction may take into account and give significant weight to (i.e., totally or partially rely upon) evaluations performed by another regulatory authority or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others

Impact of SARS-CoV-2 on vaccine development and authorisation timelines

The SARS-CoV-2 pandemic overcame many of the historical challenges that vaccine candidates face during their development and authorisation processes. Given its high health, economic, and societal impacts, it led to a change in the risk-benefit assessment of key stakeholders. This impacted standard behaviours, resulting in immediate and significant financial investments in the research and development of COVID-19 vaccines and the decision-making process, which ultimately removed some of the previously identified vaccine ecosystem barriers that impact time to market. The removal of these barriers resulted in COVID-19 vaccines being developed and authorised in one-tenth of the time compared to other vaccines. As of December 2021, just two years following the detection of the first case of SARS-CoV-2, there are 28 vaccines that have been approved by at least one country.[7] While the efforts behind SARS-CoV-2 resulted in the availability of vaccines within 12 months, the complete prioritisation of financial investments and human resources stalled vaccine research and authorisation for other diseases. The table 1 provides an overview of the identified barriers and how the SARS-CoV-2 pandemic addressed them.

Table 1: Overview of vaccine ecosystem barriers and how the SARS-CoV-2 pandemic addressed these barriers

Vaccine ecosystem barrier that impacts time to market	How the SARS-CoV-2 pandemic addressed the barrier
• Lack of recognised surrogates or correlates of efficacy. • Few regulatory authorities are able to efficiently and flexibly regulate the primary licensure of a novel vaccine. • Lack of harmonisation on requirements across regulatory authorities in countries of use.	• This barrier was not addressed by the SARS-CoV-2 pandemic due to it being a novel pathogen and insufficient research completed on SARS-CoV-1 and MERS. • More forums were used to discuss regulatory issues between regulatory authorities. Provided a platform to learn and leverage regulatory expertise. • The use of harmonisation and reliance in countries of use was leveraged for > 100 countries under the guidance of WHO.
• Lack of the possibility to share production processes and/or facilities. • Long-lead time for establishing manufacturing capacity.	• Due to the financial investments and high health, economic, and societal impacts, manufacturers made early decisions to establish and scale-up manufacturing capacity. • Manufacturers were open to and shared certain production processes.
• Lack of data for assessing the potential impact of vaccination in specific target populations. • Insufficient public budgets for the purchase and implementation of immunisation programmes.	• At the time of initial COVID-19 vaccine development, there were no other interventions that could be utilised to prevent or treat SARS-CoV-2. Vaccines were seen to play a key role to prevent the disease, ultimately reducing the burden on health systems and to provide a pathway back to 'normal' life. • Both push and pull financial mechanisms were used for vaccine development. Numerous large bi-lateral purchase agreements were made prior to the completion of the clinical trial phases and significant public financial resources were devoted to vaccine development activities.
• Lack of partners available for or capable of receiving technology transfer. • Limited availability of aligned partners to commercialise vaccines. • Insufficient access to funds for late-stage clinical development.	• Due to the high health, economic, and societal impacts, more organisations were willing to enter into vaccine development and commercialisation activities. • There was a significant amount of funding available for all phases of clinical development.

Translating lessons learned for action and investment

The SARS-CoV-2 pandemic highlighted the incredible possibilities and impact when barriers to vaccine development and authorisation were addressed. These lessons learned have the dual advantage of better preparing for a future pandemic as well as creating a more efficient approach towards vaccine research, development, and regulatory processes for epidemic and endemic diseases.

The SARS-CoV-2 pandemic highlighted the importance of pandemic preparedness to serve as a safety net and ensure that the groundwork and foundations are in place to enable rapid vaccine development and authorisation. The historical research and its outputs on coronavirus and vaccine platforms played a key role in accelerating timelines, but this research and its outputs were largely available by chance due to decades of scientific curiosity that suffered many setbacks prior to seeing success in COVID-19 vaccine development. The continued funding towards scientific advancements remains at the core, and while beneficial to pandemic preparedness it can also improve the overall vaccine ecosystem. Further, improving capabilities related to implementing smarter surveillance systems to detect pathogens, improving data collection processes and systems, appropriately training individuals to conduct data analytics, and establishing strong pathways to communicate data will all contribute to global pandemic preparedness as well as to improving the overall vaccine ecosystem.

Experts identified other key factors identified by experts as being replicable for epidemic or endemic disease vaccine development. They include:

- Ensuring financial investments focused on vaccine platforms and/or key stages during the pre-clinical and clinical development process.
- Improving communication and providing opportunities for more discussion across all stakeholders involved in vaccine research and development and the regulatory process.
- Providing flexibility in how and when data are reviewed for first authorisation, including exploring the use of streamlining reviews based on vaccine platforms and early identification of key data requirements.
- Improving regulatory harmonisation and/or regulatory reliance for authorisation in all countries of use.
- Ensuring that vaccine research and development, particularly on vaccine platforms and structural biology of diseases, receives sufficient funding and materials and new technologies are being continuously explored.
- Developing and sustaining strong and flexible research capacity and clinical infrastructure in areas with high burden of disease.
- Continuing to explore how to leverage collapsed or consolidated phases and/or conducting clinical trial phases in parallel.

While the amount and scope of financial funding made available for COVID-19 vaccines is likely only replicable in another pandemic situation, the **when and how the financial investments were made** was highlighted to impact vaccine development timelines significantly and positively. **Ensuring the availability of early funding for vaccine development was seen as an important lever that could attract other funders and allow innovative technologies to progress**. It was noted that while there are mechanisms that can provide early funding for diseases with epidemic potential, such mechanisms do not exist for supporting vaccine research and development for endemic diseases.

Further, ensuring the availability of **funding for vaccine platform technology development in addition to funding for a single vaccine candidate and improving understanding on correlates of protection** were also identified as key actions. This represents a potential shift in how vaccine research and development is financed and could positively impact the timeline and the vaccine ecosystem. When and how financial investments are deployed can help to de-risk the clinical development activities and bring several additional advantages such as ensuring end-to-end expertise, better planning at the initiation of clinical research, removing the assessment periods between clinical trial phases, and conducting activities in parallel. Having the security of financial investments can also encourage more efficient decision-making throughout the clinical development phases, and it removes a potential barrier towards market authorisation of vaccines.

While the research highlights the importance of the high level of collaboration and increased engagement with regulators, it is also recognised that the incredibly high level of regulatory engagement applied for COVID-19 would not be sustainable for all diseases. Regardless, the respondents felt that there could be lessons learned related to communication and increased collaboration between (i) regulators; (ii) vaccine developers and regulators in countries of origin; and (iii) key decision and policy makers, regulators, and vaccine developers in countries of use. The actions related to this factor include **identifying and establishing combined-advice forums** for discussions to find common ground on the process to review vaccines. One such option will be to explore a permanent regulatory forum or network of regulators similar to the established COVID-19 vaccines Regulatory Advisory Group led by CEPI and WHO. Establishing of such forums can also help to build relationships, ultimately increasing trust among all stakeholders, and provide an opportunity for the early identification of key data requirements and the standardisation of assays. These forums could also serve as a foundation to further **improve regulatory harmonisation efforts and/or encourage collaboration and discussion between regulators, and ultimately improve regulatory reliance**. As part of this, technology and the use of digital platforms may be important tools to better facilitate harmonisation and reliance efforts.

Other important actions could be to **pilot an integrated multi-functional roadmap** to provide scientific, process, and technical advice to clinical trial sponsors from regulators, **streamline certain components of the drug-development process to fully leverage existing data and evidence for vaccine platforms or use role-playing exercises**. For example, the H1N1 vaccine development efforts greatly benefited from the efforts to role-play the regulatory processes, which considered changes in strains and resulted in extremely rapid authorisation. Similar role-playing exercises could be undertaken for Disease X or other epidemic diseases, considering regional perspectives, to identify potential bottlenecks, or to identify data that could be standardised or processes to be streamlined.

The decades of research conducted on vaccine platforms, on the structural biology of protein antigens and on coronaviruses, laid a foundation that was immediately leveraged towards COVID-19 vaccine development. This played a large role in accelerating timelines, and it highlights the importance of **continued funding towards new or existing technologies to improve vaccine platforms as well as research on structural biology**. This includes **building out research streams that focus on specific virus families and end-goal vaccine design and continuing to explore recent advances in adjuvants**.

Linked to the above, this research uncovered some challenges faced during the pre-clinical and clinical research activities linked to shortages of materials needed to advance vaccine candidates. This highlights the importance of **having established animal models in key diseases where the data is public and available, generating data from various pathogens on different vaccine platforms, and ensuring sufficient manufacturing capacity to produce clinical trial materials.**

Call to action

The SARS-CoV-2 pandemic triggered concerted action by governments, funders, regulators, and industry that overcame many of the historical challenges that vaccine candidates usually face during the development and authorisation process. These challenges include financial, regulatory, manufacturing, clinical, market and policy barriers.

Action to remove these barriers resulted in six highly effective COVID-19 vaccines being safely developed and authorised for use in less than one year, 10 times faster compared to the average timelines for developing vaccines for other infectious disease threats.

We call on governments and funders to learn from the lessons of the SARS-CoV-2 pandemic and take the following actions to build a more efficient and effective vaccine ecosystem that can protect us from other pandemic, epidemic, and endemic disease threats.

1. **Commit sustained financial support for scientists and foundational science** for the full vaccine design and development process, prioritising investment in:
    - Understanding pathogen biology including structural biology.
    - Developing predictive model systems for key diseases.
    - Advancing rapid, flexible vaccine technology platforms such as mRNA and viral vectors.
2. **Establish strong clinical trial infrastructure** in regions of infectious disease burden
    - Ensuring sufficient manufacturing capacity is available to produce vaccine doses for clinical trials.
    - Building sustainable research capacity to conduct vaccine trials.
    - Building regulatory capacity in countries of highest disease burden to support, conduct, and approve clinical trial processes.
    - Implementing smarter surveillance systems, improving data-collection and data-sharing systems, increasing data analytics capacity, and using such data to inform clinical trial design for vaccine efficacy and effectiveness studies.
3. **Support and strengthen global funding mechanisms** to de-risk and advance development of vaccines for pandemic and endemic diseases, including:
    - Meeting CEPI's $3.5 billion replenishment target to support its mission to condense new vaccine development timelines for pandemic disease threats to 100 days.
    - Identifying effective funding mechanisms to support early-stage R&D for key endemic diseases and guarantee demand for such vaccines to ensure successful development.
4. **Facilitate communication** between regulatory authorities and other stakeholders by developing forums for:
    - Promoting open discussion between regulators in different regions and support regulatory harmonisation and capacity development.
    - Promoting open discussion between regulators and vaccine developers and between vaccine developers, manufacturers, and policymakers in countries of use.
    - Developing and releasing comprehensive guidance documents and provide opportunities to role-play situations.

As the world considers how it can strengthen its response to major infectious disease threats in the future, it is critical that we learn from the SARS-CoV-2 pandemic and invest in the necessary infrastructure to improve capacity, efficiency, and success in the development of vaccines for other infectious diseases. By committing to sustainable investment in research, strengthening clinical trial infrastructure, de-risking vaccine development, and facilitating better communication between regulatory authorities and other key stakeholders, we can help build a world that is better prepared to prevent and eliminate infectious diseases.

Annexes

Annexe 1: Detailed methodology to identify factors

To identify the factors that contributed to the rapid clinical development and approval of COVID-19 vaccines and determine which factors, if any, could be applied to future vaccine development for epidemic and endemic vaccines, a mixed-methods research approach was employed which included a rapid literature assessment, a virtual survey, and interviews.

Rapid assessment of literature

Methodology

A rapid assessment of published and public information sources was performed to identify all potential factors that may have impacted the timelines for COVID-19 vaccine development and approval. The desk review consisted of four components: (i) identification of peer-reviewed articles on PubMed, Embase, Medline, Ovid, ScienceDirect; (ii) identification of recent but not yet peer-reviewed articles on the preprint server medRxiv; (iii) identification of clinical trials registered on clinicaltrials.org; and (iv) targeted review of public information sources including key partner websites (WHO, CEPI, Gavi, UNICEF, etc.), news articles (e.g., country commitments to purchase, etc.), manufacturer press releases, and publicly available dashboards on COVID-19 vaccines. The literature search was limited to documents published between 1 January 2002 and 31 May 2021.

For published literature, search terms were developed and exclusion criteria were applied when searching and reviewing published literature. In some instances, in order to identify the most relevant information, more targeted searches were conducted (i.e., adaptive trials). A total of 2,142 articles were identified for inclusion in the initial title and abstract reviews. The search terms deployed are detailed below in Table 2.

Table 2: Published literature search terms

Dimension	Search Term
Nature and impact of the SARS-CoV-2 pandemic	(Economic impact OR health impact) AND (SARS-CoV-2 OR COVID-19) AND vaccine AND Global AND (“2019/11/1”[Date - Publication]: “3000”[Date - Publication]) AND Review
	(((excess deaths) AND (COVID-19)) AND (global)) AND ((“2021/01/01”[Date - Publication]: “3000”[Date - Publication]))
	((Vaccine demand OR market size) AND COVID-19 AND vaccine) NOT (Vaccine demand OR market size AND COVID-19 vaccines)
	(((Vaccine AND Data sharing OR Open Access) AND (COVID-19 OR SARS-CoV-2)) AND (Review[Publication Type])) AND ((“2019/11/01”[Date - Publication]: “3000”[Date - Publication]))
Financial investment and outcomes	(Financial investment OR commitment) AND COVID-19 AND (vaccine OR vaccine development)
	((operation warp speed) AND (Covid-19)) AND (vaccine)
	((((COVID-19 vaccine) AND (investment) OR (COVAX)) AND ((“2019/11/01”[Date - Publication]: “3000”[Date - Publication]))) AND (Review[Publication Type])

Dimension	Search Term
Clinical development	((Phase I clinical trial) OR (Phase II clinical trial) OR (Phase II/III clinical trial) OR Phase III clinical trial)) AND SARS-CoV-2 AND vaccine
	(clinical trial[Publication Type]) AND SARS-CoV-2 AND vaccine
	(Coronavirus AND vaccine NOT COVID-19) AND (Review[Publication Type]) NOT poultry
	(((Phase I clinical trial) OR (Phase II clinical trial) OR (Phase II/III clinical trial) OR Phase III clinical trial)) AND vaccine AND MERS AND coronavirus NOT COVID-19
	Coronavirus AND vaccine AND pre-clinical – limited to publications prior to 2018
	((Clinical trial) AND vaccine AND (lessons learned OR accelerate)) AND (SARS-CoV-2 OR COVID-19))
	(Vaccine AND Adaptive AND ("clinical trial, phase I"[Publication Type] OR "clinical trial, phase II"[Publication Type]))
	((Clinical trial) AND vaccine AND (innovation OR adaptive)) AND (SARS-CoV-2 OR COVID-19))
	(((vaccine) AND (clinical trial phase I OR clinical trial phase II OR clinical trial phase III)) AND (Adaptive AND (group sequential design OR sample size OR enrichment OR treatment arm OR patient allocation OR endpoint selection OR multiple design))) AND (review[Publication Type]) *Each italicised term was also searched individually
	(((Drug OR Therapeutic) AND Adaptive AND ("clinical trial, phase I"[Publication Type] OR "clinical trial, phase II"[Publication Type]) OR "clinical trial, phase III"[Publication Type]))) AND (AND COVID-19)) AND (("2019/11/01"[Date - Publication]: "3000"[Date - Publication]))
	((Clinical trial) AND vaccine AND innovation) AND (SARS-CoV-2 OR COVID-19))
	((SARS AND vaccine) NOT (SARS-COV-2 OR COVID-19)) – limited to publications prior to 2006
	(((Phase I clinical trial) OR (Phase II clinical trial) OR (Phase II/III clinical trial) OR Phase III clinical trial)) AND vaccine AND MERS AND coronavirus NOT COVID-19
	Coronavirus AND vaccine AND pre-clinical – limited to publications prior to 2018
	(Coronavirus AND vaccine NOT COVID-19) AND (Review[Publication Type]) NOT poultry – limited to publications prior to 2018
Regulatory review and processes	(((((Emergency use approval) OR (Regulatory pathway) OR (Marketing authorisation) OR (Facilitated approval procedure) OR (Reliance mechanisms))) AND ((COVID-19 vaccines))) AND (("2019/11/01"[Date - Publication]: "3000"[Date - Publication]))) AND (Review[Publication Type])

For pre-print literature, searches were performed in medRxiv for articles pertaining to COVID-19 vaccines. A total of 1,043 articles were identified and extracted. Proximity searches were subsequently performed using Adobe software using search terms similar to those for published literature in order to identify articles for each dimension. The proximity searches were conducted using a range of up to five words. Table 3 presents the proximity search terms used for pre-print literature.

Table 3: Proximity search terms for pre-print literature

Dimension	Search Terms
Nature and impact of the SARS-CoV-2 pandemic	Economic impact
	Health impact
	Market size
	Data sharing
Financial investments and outcomes	Government finance/financing
	Innovative finance/financing
Clinical development	Vaccine innovation
	Phase I/Phase II/Phase III
	Adaptive trial
	Group sequential design
	Factorial
	Sample size
	Enrichment
	Treatment arm
	Patient allocation
	Endpoint selection
	Multiple design
Regulatory review and processes	COVID-19 vaccine regulatory

Results

The results from the published and pre-print literature were combined. An initial screening of all titles was performed to assess article relevance and exclude articles not relevant within the scope of the project. The full text review was performed for all 388 published articles (Table 4), and 42 pre-print articles identified as relevant and key information were extracted and recorded.

Table 4: Literature identified for full text review

Dimension	Rationale	Final results
Nature and impact of the SARS-CoV-2 pandemic	Articles were excluded if they did not provide any information on the health, economic, and social impacts of the SARS-CoV-2 pandemic.	33
	Articles were excluded if they did not relate to the sharing of information, open science, or provided information only on networks/platforms.	9
Financial investment and outcomes	Articles were excluded if they did not provide any financial-related information.	27
Clinical development and good manufacturing practices	74 articles prior to 2019 were included as part of the landscape review for SARS-CoV-1. See below.	85
	Articles were excluded when the focus was not on COVID-19-related pharmaceutical interventions.	31
	Reviewed for key characteristics of previous coronavirus research and development that may have impacted the development of COVID-19 vaccines.	192
Regulatory review and authorisation	Articles were excluded when the focus was on clinical development rather than on the underlying regulatory processes.	11

The rapid literature assessment resulted in a selection of 23 factors that were further evaluated and validated by an online survey and interviews. Table 5 provides an overview of the identified factors.

Table 5: Factors impacting COVID-19 vaccine development and authorisation timelines identified per the rapid literature assessment

Dimension	Factor description
Nature and impact of SARS-CoV-2 pandemic	Significant health, economic, and social impacts to high-income countries.
	Unprecedented demand for COVID-19 vaccine generated by high SARS-CoV-2 burden.
	The global market which targets the majority of the population and may require repeated booster vaccination.
	Researchers were more open to sharing preliminary findings and information.
Financial investments and outcomes	Unprecedented financial investments from multiple funding sources were made in research and clinical development.
	Materially large advance purchase agreements made with countries prior to the completion of clinical trials.
	Pooling/coordination of financial resources to create an attractive global market across donors, multi-lateral agencies and within governmental agencies.
Clinical development	Clinical trials were designed with collapsed/consolidated phases (e.g., Phase I/II or Phase II/III).
	High SARS-CoV-2 transmission rates in clinical trial sites.
	Master clinical trial protocols were collaboratively developed, published, and utilised by trial sponsors, partners and stakeholders.
	Trial sponsors and stakeholders conducted additional activities to ensure high participant enrolment (e.g., specific community outreach).
	Use of innovative statistical approaches (e.g., Bayesian approaches to measure endpoints).
	Strong and flexible research capacity and clinical trial infrastructure in areas with high burden of disease.
	Decades of prior research into vaccine platforms allowed for immediate use (e.g., viral vector, nucleic acid).
	Pre-existing vaccine development research on SARS-CoV-1 and MERS which identified the potential mode of action for candidate COVID-19 vaccines.
	SARS-CoV-1 and MERS were previously studied extensively in animal models.
Regulatory authority and pathways	Study requirements and non-clinical standards (e.g., pharmacology, toxicology) were pre-defined, communicated, and used.
	Regulatory authorities limited data requirements to those essential for emergency use authorisation within the context of a pandemic.
	Regulatory limited data requirements to those essential for emergency use authorisation from a manufacturing perspective.
	Regulatory authorities provided flexibility on the sequencing of steps to assess safety, immunogenicity, and efficacy.
	Regulatory authorities adopted accelerated review processes and prioritised their reviews.
	Regulatory authorities maintained a high focus on safety, but accepted uncertainty on the long-term effects of COVID-19 vaccines.
	Emergency use authorisation or conditional approvals were used to ensure rapid availability of vaccines.

Stakeholder survey and interviews

Methodology

Relevant stakeholders for consultation were mapped based on gender, geographic location, and areas of expertise to ensure adequate representation of all key stakeholders, perspectives and expertise.

Individuals were invited to either participate in the interviews or online survey. The online survey's key objective was to rate the identified factors from the desk review. For the online survey, the respondents were asked to rate each identified factor using a Likert scale of "Extremely important" to "Not important at all". Each response was assigned point values between 1 (Not important at all) and 5 (Extremely important). The weighted averages were calculated for each factor, and the factors were ranked relative to each other based on their weighted averages. This analysis was also stratified to consider the different perspectives of those working in vaccine manufacturing and those not. Further, the survey respondents were given a series of open-ended questions to identify additional factors not previously captured. Qualitative information provided in open-ended survey questions was analysed and used to supplement the quantitative findings as well as to identify any additional factors.

The interviews were largely used to identify other key factors not identified per the desk review, and to qualitatively determine the role and level of importance that different factors played in COVID-19 vaccine development and authorisation. Interview guides were developed, and questions were tailored to different groups of stakeholders based on their subject matter expertise. Interviews were transcribed verbatim. Thematic analysis of the interview responses began with a detailed review of all interview notes and statements. These were organised according to the four primary dimensions (pandemic context, unprecedented financial investment, proactive regulatory approach, and faster clinical development). Internal project team discussions were convened to ensure that interview responses were correctly interpreted and categorised, and key nuances were captured. Interview transcriptions were re-reviewed for clarity until agreement was reached within the internal project team. Based on interview responses, new factors were added to those previously identified per the literature.

Results

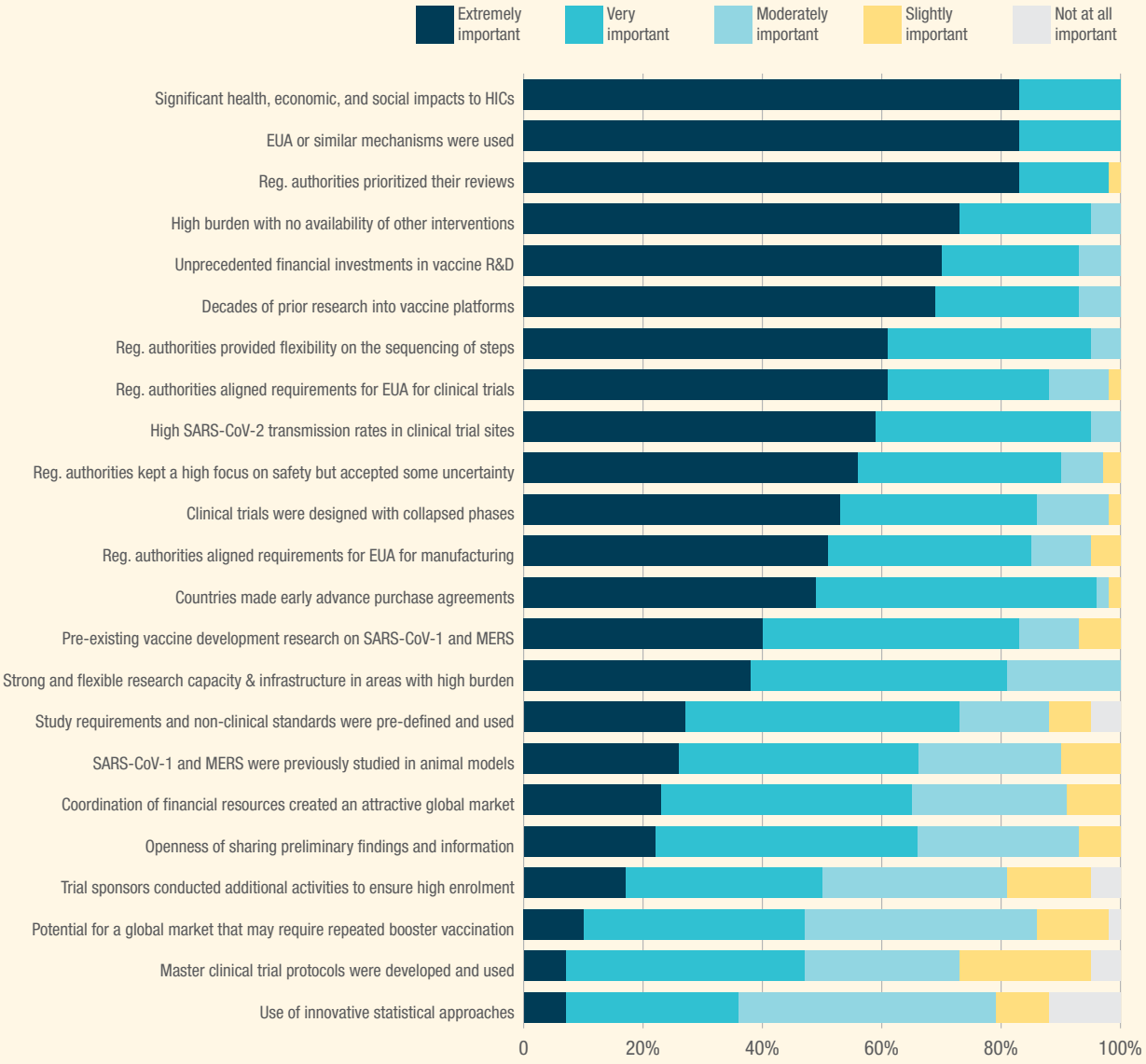
Figure 11 provides the results of the survey responses and how the respondents rated each identified factor. The stratified analyses did not show significant differences between the responses and thus is not presented separately.

The factors had a range of mean scores from 3.10 to 4.83 and a median of 4.36. Of the factors that scored above the median, 50% of pandemic context factors (2 of 5), 66% of financial factors (2 of 3), 33% of clinical development factors (3 of 9), and 71% of regulatory factors (5 of 7) scored above the median. Further, 80% of the respondents indicated that the identified factors could be replicable, highlighting that more flexibility and efficient regulatory reviews, greater engagement and collaboration from regulators, trial design and pathways, and financial de-risking were important factors that could be replicable in other situations.

While the interviewees were not asked to rate the factors, all 46 interviewees indicated the importance of the proactive regulatory approach taken highlighting that it was both the way of working as well as the clear communication of data requirements. The interviewees identified key themes, including the high levels of collaboration between regulators and vaccine trial sponsors, high prioritisation by regulators, use of emergency use authorisation or similar processes, and flexibilities (e.g., rolling reviews, accepting certain data points prior to others, etc). Further, all of the interviewees also highlighted the importance of the pandemic context that resulted in high levels of political will, high levels of financial investment, and high prioritisation and the reallocation of human resources towards COVID-19 vaccines.

The respondents consistently identified other key themes, including the early financial investments in vaccine research as well as having available funding through existing mechanisms, such as CEPI or BARDA. Many indicated that the financial investments de-risked the decision-making on vaccine development, as the risk of failure was

Figure 11: Results of ranking of identified factors from the online survey



shared among all stakeholders. Finally, the interviewees also indicated that the historical research and experience on coronaviruses and other epidemic diseases as well as the prior work on vaccine platforms were invaluable.

Both the survey and interviewees provided additional factors that impacted timelines but were not identified per the rapid literature assessment. These factors included rapid and clear decision-making, use and strength of partnerships, high levels of political will, high levels of trust between key stakeholders, the clear age difference on the severity of disease, high levels of expertise that were prioritised not only towards vaccine research and development but also for regulatory authorisations, changes in risk-benefit assessments of key stakeholders, financial investments that de-risked late-stage development, and the use of forums or working groups.

The feedback from the consultations resulted in a selection of 32 key factors that impacted the timelines for vaccine development and authorisation, as seen in Figure 9.

Annexe 2: Evidence matrix to assess identified factors

Using the data collected from the rapid literature assessment, survey, and interviews, a level of confidence was assigned to each factor to indicate its perceived contribution to the accelerated timelines for COVID-19 development and authorisation. The table 6 provides an overview of how the level of confidence was assigned to each factor.

Table 6: Level of evidence matrix

Rank	Description of confidence categories	Approach
High confidence	The evidence/data is viewed as more factual than subjective and is strongly supported by the literature, experts, and stakeholders.	Evidence/data is stated in all different sources with good triangulation of the conclusions, and the sources are of decent quality, e.g., if the same evidence or data is stated in all three sources (literature review, interviews, and the survey), stated multiple times within the sources, and the conclusions reached are the same or similar.
Moderate confidence	The evidence/data is viewed as reasonable and is supported by the majority of the literature and experts. However, there may be some conflicting perspectives that should be noted and may require additional exploration.	Evidence/data is stated in at least two data sources but there is less triangulation of the conclusions, and the sources are of lesser quality, e.g., if the same evidence or data is stated in the literature review, the survey, but not by the interviews, and there are some different conclusions across the three sources.
Low confidence	The evidence/data is viewed as less reasonable with some support from the literature and experts. This evidence/data may be viewed as more subjective than factual and may require additional efforts to strengthen the evidence/data.	Evidence/data is stated only in one or two of the sources with limited triangulation and the sources are of lesser quality, e.g., if the same evidence or data is stated only in one or two of the data sources, and the conclusions across the different sources are not aligned.
Very low confidence	It is not clear if the evidence/data should be viewed as reasonable, and evidence/data has been stated only by one person. The evidence should be viewed as subjective and will require additional efforts to strengthen the evidence/data (e.g., use of the focus groups).	Evidence/data is stated in only one of the sources and by one person.

Annexe 3: Regression analysis

Overview of the methodology

The WHO COVID-19 vaccine tracker and landscape database was used to identify COVID-19 vaccine candidates: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. The analysis used the database current as of 17 September 2021. This contained 118 vaccines in clinical trials with an assigned WHO ID. The ID numbers are assigned in order of incorporation into the database (primarily the order in which Phase I vaccine trials were registered in trial databases such as ClinicalTrials.gov). Of the 118 candidate vaccines, 102 were included in this analysis. The remaining 16 vaccines were excluded because they were duplicates of the same vaccine or were further developments of vaccines already in the database (e.g., ID 93, is an mRNA vaccine developed by Moderna, based on its registered vaccine), designed to target new Variants of Concern.

The reliability of the WHO database was checked by matching vaccines in available clinical databases (e.g., ClinicalTrials.gov), and in pre-prints and PubMed with the vaccines in the WHO database. These searches failed to find significant omissions or additions to the WHO clinical database for vaccines in clinical trials. On the other hand, similar searching of literature sources showed that the WHO pre-clinical database listed approximately only half the vaccines not yet in clinical trials, identified in the literature and this pre-clinical database has not been used in this analysis. This probably reflects very different entry criteria into these databases, with the latter apparently relying on self-reporting, whereas the clinical database is triggered by entries in clinical trial site databases that are actively monitored by WHO.

Based on the information in the WHO clinical landscape database, vaccines were scored on a 0 to 5 scale as follows (Table 7):

Table 7: Scoring for vaccines

Score	Criteria
0	In the database, but no results posted yet from a Phase I study
1	In Phase II
2	In Phase III
3	Phase III completed but no emergency use authorisation or registration in any country
4	Phase III completed and authorised for emergency use or registered
5	Phase III completed, authorised for emergency use, or registered and widely deployed, e.g., in multiple countries

Note that this score is based on the progress through Phase I, II and III and not on when emergency use authorisation was granted. Five vaccines that received emergency use authorisation before the conclusion of Phase III (WHO ID: 11,14, 24, 32 and 66, e.g., the COVIran Barekat vaccine in Iran). These received a score commensurate with the stage of Phase I/II/III trials, even if the vaccine had been deployed. Where combined trials (e.g., Phase I + II) were undertaken, vaccines were scored according to the most advanced data that had been released (i.e., a vaccine could score a "1" even if the combination Phase I + II had not been completed).

Multiple sources of evidence were used in determining the score. They included:

- Press releases on the company website
- Other press reports
- Data from websites
- Data from regulatory agencies
- Pre-prints (medRxiv was systematically searched)
- Published papers
- Dates for recruitment, etc., posted in clinical trial registries (mainly used to limit the possible stage of development on the 17 September 2021)

Scoring of factors

Nine factors were chosen for the initial analysis. These were chosen to explore major variables summarised in the Introduction: the type of vaccine (vaccines that require extensive downstream development e.g., protein vaccines or vaccines that do not (e.g., viral vectored vaccines); the regulatory environment; the size of the pre-clinical group (as judged by the number of authors or institutes) on pre-clinical/Phase I papers; the use of innovative clinical trial developments as judged by the use of combination vaccine trials; the size and experience of a manufacturing partner (established vaccine manufacturers or manufacturer's size); and the source of funding.

For each factor for each vaccine, the factor was scored as a +1 or a -1, as detailed in the following table. For convenience, the -1 generally refers to the score with the "smaller" factor, e.g., number of authors, but the assignment of a -1 or a +1 is purely arbitrary and has no impact on the regression, other than the sign of the coefficient.

Table 8 provides an overview of the factors and how they were scored.

Table 8: Overview of factors and scoring methodology

Factor	Score	Criteria
Vaccine Type	-1	Recombinant protein (soluble, VLP, etc.)
	+1	Inactivated virus or Antigen delivered as nucleic acid (DNA, RNA, viral vector)
Regulatory Agency	-1	Not on list of WHO Stringent Regulatory Agencies[5]
	+1	On list of WHO Stringent Regulatory Agencies
No. of authors on Pre-clinical/Phase I paper	-1	Less than the median value of 15 authors for the overall dataset
	+1	15 or more authors listed
No. of institutes on Pre-clinical/Phase I paper	-1	Less than the median value of 4 institutes for the overall dataset
	+1	4 or more institutes listed
Pre-clinical or Phase I data available	-1	No pre-print, paper etc., found after detailed searching
	+1	Pre-print or paper found describing pre-clinical or Phase I data
Use of combination trials as specified in the WHO landscape	-1	No combination trials listed
	+1	At least one combination trial listed
Source of funding	-1	Private company funds or no available data
	+1	At least some government or other grant funding
Established vaccine manufacturing partner	-1	Manufacturing partner with no licensed vaccine
	+1	Manufacturing partner with at least one licensed vaccine
Size of manufacturing partner	-1	Small manufacturing partner, generally biotech start-ups or small-medium-sized enterprise
	+1	Large manufacturing partner

5. https://www.who.int/initiatives/who-listed-authority-reg-authorities/SRAs

Data sources

The data sources used to inform the evaluation and scoring of each factor for the vaccine candidates included for analysis are described below:

- **The vaccine type and the use of combination trials:** taken directly from the WHO database.
- **The type of regulatory agency:** determined by the country of the trial sponsor from the appropriate clinical trial register (all vaccines in the WHO database have at least one entry in an established clinical trial database).
- **Number of authors or institutes on pre-clinical or Phase I trial paper and data availability:** extensive searches were done in PubMed, in the bioRxiv, medRxiv and other pre-print servers, and using Google, to identify papers or preprints describing preferably pre-clinical or Phase I trial data. Searches were conducted for the name of the vaccine, for the institutes or companies listed in the WHO database. Where no paper could be found, the number of authors and the number of institutes were scored as zero.
- **Use of combination trials**
- **Funding:**
    - Acknowledgement of grants or other funding on pre-clinical/clinical trial papers.
    - Nature of the institutes undertaking the work (e.g., funding of COVID-19 vaccine at government research institutes was assumed to be at least in part government funding).
    - Statements by commercial company, (e.g., statement by Pfizer that the work was only internally funded).
    - Search of the U.S. National Institutes of Health funding database.
    - Press releases or other data on company websites.
    - Where no data could be found, and no developer was a government agency (e.g., ID 20), funding was assumed to be non-government (i.e., score -1).
- **Manufacturer vaccine experience and size:** primarily from company websites.

Analysis

Data were entered into an Excel spreadsheet, and the analysis was done using the "Blank Spreadsheet" option of Design-Expert v13 software from Stat-Ease, Inc., with the following parameters:

- 9 categorical variables with levels -1 and +1
- 102 rows, comprised of the vaccine candidates included for analysis

Data were copied from the Excel file into the input array. No transformations were selected for the dependent variable. Multiple methods built into Design-Expert v13 were used to simplify the model. All methods started using a quadratic order. The methods used included:

- Maximising adjusted R^2
- Progressively adding terms with the smallest p value
- Progressively deleting terms with the largest p value
- Maximising the Akaike information criterion by forward addition of terms
- Maximising the Akaike information criterion by reverse subtraction of terms
- Maximising the Bayesian information criterion by forward addition of terms
- Maximising the Bayesian information criterion by reverse subtraction of terms

Depending on the method for simplification, factors were either deleted or added if they made a statistically significant change to the optimisation parameter under consideration (e.g., for optimising based on the adjusted R^2, parameters were deleted if their deletion did not significantly lower the adjusted R^2). In the first model shown below, primary factors, e.g., NRA type, that were not significant had to be added back to the model to maintain the hierarchy (i.e., NRA was needed if the interaction between NRA and vaccine manufacturer was retained).

The preferred model was tested with a panel of goodness of fit tests available within the Design Expert software.

Results

A two-level factorial regression of the level of advancement of each vaccine versus a series of factors hypothesised to impact on the speed of development was developed to complete the findings from the desk review, survey, and interviews.

In the selected model there were four primary factors, all of which were highly significant, and three interactions (Table 9).

Table 9: Results from selected regression model

Primary factor			Interactions		
Factor	**Coefficient**	**P value**	**Interaction**	**Coefficient**	**P value**
Number of institutes	0.10	0.0003	No. institutes + combined trials	0.10	0.0009
Use of combined trials	0.10	0.0002	No. institutes + vaccine manufacturer	0.10	0.0012
Vaccine manufacturer	0.12	0.028	Combined trials + manufacturer size	0.10	0.0048
Manufacturer size	0.12	0.021			

Coefficient is a measure of the impact of the factor or interaction.
P value is the probability that the coefficient is not zero.

The p value for the model was <0.0001, showing that the model as a whole is highly significant as well as the individual factors and interactions listed in Table 9. As judged by the coefficients, each factor and interaction had a similar impact on the rate of vaccine progression (e.g., having a manufacturing partner who had previously developed and marketed a vaccine was roughly as important as the use of combination trials). As expected from this type of minimal model, the fit only accounts for some of the differences in the progress of different vaccines. Specifically, an adjusted R^2 of 0.49 indicates that the model accounts for just under a half of the variance in the score, after adjusting for the number of factors in the regression model. Some of the residual variation will be random (e.g., chance in picking a vaccine target), but some will be for factors not included in the model and that may not be readily measurable (e.g., individual brilliance of scientists involved, the entrepreneurship of the leadership).

Through the regression analysis, the impact of several key factors identified in previously detailed project analyses was corroborated:

- **Use of combination trials** as part of the development programme was highly associated with rapid development and with the standard model and was the single most significant factor. It had the largest coefficient and the smallest p value. This factor aligns with the findings from the appraisal of literature and consultations on the impact of the increased use of phased trials, de-risking of the clinical trials, and removal of standard assessment periods between each phase.
- **The number of institutes** that formed part of the pre-clinical/Phase I study team closely followed use of combined trials as the next most important factor. This shows that the size and diversity of the pre-clinical/Phase I collaboration was a critical part of early COVID-19 vaccine development

success. This factor speaks to the importance of partnerships, in alignment with the consultations, which highlights the ability to leverage different skills and expertise of relevant stakeholders, and the level of prioritisation of skilled and knowledgeable human resources towards the development and approval of COVID-19 vaccines by all relevant stakeholders.

- **Manufacturer involved had previously developed and manufactured licensed vaccines and the size of the manufacturer** were both important. This highlights the importance of prior vaccine experience in navigating the processes for development and approval.

Surprisingly, the vaccine type was consistently found not to be significant in its influence on the progression of COVID-19 vaccines. This suggests further areas for investigation beyond this factorial analysis, including a review of the vaccine type distribution in pre-clinical studies, as many additional vaccines using mRNA technology may be entering development at a later point. This may obscure the importance of vaccine type on the fastest progressing vaccines, none of which were recombinant protein-based vaccines.

Key factors identified by the regression analysis and also through the literature assessment, survey, and interviews included the experience of the vaccine developers and manufacturing partners involved in clinical development and the use of combined trial phases between Phases I-III. Interestingly, the regression analysis did not identify significant factors related to the financial investments or regulatory practices employed to support COVID-19 vaccine development. However, a key limitation of the regression analysis is the availability and quality of quantitative data. Therefore, a lack of significant factors in these areas is not evidence to support that these factors did not play critical roles in the development of COVID-19 vaccines.

Bibliography

1. Thomas DW, Burns J, Audette J, Carroll A, Dow-Hygelund C, Hay M. Clinical Development Success Rates 2006-2015. USA: Biotechnology Innovation Organization (BIO), Biomedtracker, and Amplion, 2016.
2. DiMasi JA, Florez MI, Stergiopoulos S, et al. Development Times and Approval Success Rates for Drugs to Treat Infectious Diseases. Clin Pharmacol Ther 2020; 107(2): 324-32.
3. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econ 2016; 47: 20-33.
4. Pronker ES, Weenen TC, Commandeur H, Claassen EH, Osterhaus AD. Risk in vaccine research and development quantified. PLoS One 2013; 8(3): e57755.
5. DiMasi JA, Feldman L, Seckler A, Wilson A. Trends in risks associated with new drug development: success rates for investigational drugs. Clin Pharmacol Ther 2010; 87(3): 272-7.
6. Mavolti S, Malhame M, Gilchrist S, Ogden L. Effective Vaccine Ecosystem. London, U.K.: Wellcome Trust, 2020.
7. Basta NE and Moodie EMM on behalf of the Vaccines Infectious Disease Prevention and Epidemiology Research Group [VIPER]. COVID-19 Vaccine Development and Approvals Tracker. 2020. https://covid19.trackvaccines.org/vaccines/approved/ (accessed 9 December 2021).
8. The true death toll of COVID-19: Estimating global excess mortality. 2020. https://www.who.int/data/stories/the-true-death-toll-of-covid-19-estimating-global-excess-mortality (accessed January 18 2022).
9. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. 2022. https://covid19.who.int/ (accessed January 18 2022).
10. Dept. IMFR. World Economic Outlook, April 2020 : The Great Lockdown, 2020.
11. Sheek-Hussein M, Abu-Zidan FM, Stip E. Disaster management of the psychological impact of the COVID-19 pandemic. Int J Emerg Med 2021; 14(1): 19.
12. Dye T, Levandowski B, Siddiqi S, et al. Non-medical COVID-19-related personal impact in medical ecological perspective: A global multileveled, mixed method study. medRxiv 2021: 2020.12.26.20248865.
13. Clinical trial data for COVID-19 vaccines. In: National Library of Medicine, editor. United States: National Institute of Health,; 2021.
14. Policy Cures Research. G-Finder survey. 2021. https://gfinder.policycuresresearch.org/ (accessed September 2021).
15. Barr L. Tuberculosis Research Funding Trends, 2005-2019. New York, USA: Treatment Action Group, 2020.
16. Pneumococcal AMC. Geneva, Switzerland: Gavi, the Vaccine Alliance, 2021.
17. Gruber WC, Scott DA, Emini EA. Development and clinical evaluation of Prevnar 13, a 13-valent pneumococcal CRM197 conjugate vaccine. Ann N Y Acad Sci 2012; 1263: 15-26.
18. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Reference Life Table. Seattle, United States of America: Institute for Health Metrics and Evaluation (IHME); 2021.
19. Global tuberculosis report. Geneva: World Health Organization, 2020.
20. Clinical trial data for tuberculosis vaccines. In: National Library of Medicine, editor. United States: National Institute of Health,; 2021.
21. Global Health Estimates 2019: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2019. Geneva: World Health Organization; 2020.
22. 2009 H1N1 Pandemic Timeline. 2019. https://www.cdc.gov/flu/pandemic-resources/2009-pandemic-timeline.html (accessed October 2021).
23. European Medicines Agency. Vaccines for pandemic influenza: Pandemic preparedness vaccine. 2022. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/pandemic-influenza/vaccines-pandemic-influenza#pandemic-preparedness-vaccine-section (accessed January 19 2022).
24. Minor PD. Vaccines against seasonal and pandemic influenza and the implications of changes in substrates for virus production. Clin Infect Dis 2010; 50(4): 560-5.
25. Harrington WN, Kackos CM, Webby RJ. The evolution and future of influenza pandemic preparedness. Exp Mol Med 2021; 53(5): 737-49.
26. Adjuvant-containing H1N1 influenza vaccine pandemrix: narcolepsy in children. Prescrire Int 2011; 20(117): 154.
27. Reed SG, Orr MT, Fox CB. Key roles of adjuvants in modern vaccines. Nat Med 2013; 19(12): 1597-608.

Wellcome supports science to solve the urgent health challenges facing everyone. We support discovery research into life, health and wellbeing, and we're taking on three worldwide health challenges: mental health, global heating and infectious diseases.

MMGH Consulting GmbH is an independent advisory firm supporting public and non-profit clients to translate scientific evidence, data, and knowledge into strategies and actions directly impacting people's health.

Wellcome Trust, 215 Euston Road
London NW1 2BE, United Kingdom
T +44 (0)20 7611 8888, Email: contact@wellcome.org
wellcome.org

MMGH Consulting GmbH, Kuerbergstrasse 1
8049 Zurich, Switzerland
T +41 44 553 04 53, Email: info@mmglobalhealth.org,
mmglobalhealth.org