Factors, enablers and challenges for COVID-19 vaccine development

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ABSTRACT
The COVID-19 pandemic triggered a sense of vulnerability and urgency that led to concerted actions by governments, funders, regulators and industry to overcome traditional challenges for the development of vaccine candidates and to reach authorisation. Unprecedented financial investments, massive demand, accelerated clinical development and regulatory reviews were among the key factors that contributed to accelerating the development and approval of COVID-19 vaccines. The rapid development of COVID-19 vaccines benefited of previous scientific innovations such as mRNA and recombinant vectors and proteins. This has created a new era of vaccinology, with powerful platform technologies and a new model for vaccine development. These lessons learnt highlight the need of strong leadership, to bring together governments, global health organisations, manufacturers, scientists, private sector, civil society and philanthropy, to generate innovative, fair and equitable access mechanisms to COVID-19 vaccines for populations worldwide and to build a more efficient and effective vaccine ecosystem to prepare for other pandemics that may emerge. With a longer-term view, new vaccines must be developed with incentives to build expertise for manufacturing that can be leveraged for low/middle-income countries and other markets to ensure equity in innovation, access and delivery. The creation of vaccine manufacturing hubs with appropriate and sustained training, in particular in Africa, is certainly the way of the future to a new public health era to safeguard the health and economic security of the continent and guarantee vaccine security and access, with however the need for such capacity to be sustained in the interpandemic period.

INTRODUCTION
Vaccines are among the most cost-effective public health interventions currently available. Together with antibiotics and clean water, vaccination against infection and disease has saved millions of lives and increased life expectancy in all countries.1 2 The discovery of SARS-CoV-23 and the global COVID-19 pandemic4 were rapidly followed by unprecedented multinational efforts to develop vaccines to prevent infection and severe disease, turn the pandemic tide, and mitigate the devastating economic and societal damages associated with SARS-CoV-2.5

Clinical development and approval of vaccines typically take 5–10 years, and only 10% of vaccine candidates receive market authorisation.6 7 However, the COVID-19 pandemic became a radical game changer as in less than a year from the detection of the first SARS-CoV-2 case, emergency use authorisation (EUA) was granted to at least six vaccines. Two years later, 36 vaccines had been approved by at least one country.8 Identifying and understanding the impact of the factors that enabled the rapid clinical development and EUA of COVID-19 vaccines may shed light on lessons learnt to streamline vaccine development for emerging pandemics and pathogens.9 11
Several factors increased the speed of vaccine development: pandemic urgency, unprecedented financial investment, massive and sustained demand, building on past research investments, expedited regulatory review and accelerated clinical testing. Scale-up and manufacturing at risk with pharmaceutical companies beginning to mass produce vaccines in parallel with clinical trials rather than waiting for regulatory approval are important accelerators of vaccine availability. This strategy, assisted by government investments, results in significant financial risk to the funder as large investments are made before safety and efficacy of a vaccine are demonstrated. Still another factor was that the accelerated development of COVID-19 vaccines built on two decades of research for other pandemic coronavirus threats such as severe acute respiratory syndrome and Middle East respiratory syndrome (MERS) that demonstrated how the spike protein or its receptor-binding domain was a prime target for any vaccine development strategy. Such discoveries allowed the pharma companies and the community of virological researchers to ‘hit the ground running’ when the COVID-19 sequence became available in January of 2020.

**Pandemic urgency**

The impact of the COVID-19 pandemic was major at health, economic and social levels worldwide. The world has become aware that the full impact of the pandemic has reached areas and magnitude far greater than reported COVID-19 deaths alone. Although reported COVID-19 deaths between 1 January 2020 and 31 December 2021 reached almost 6 million worldwide, estimates suggested instead that the number of deaths worldwide may be 18.2 million (measured by excess mortality). The clinical impact of COVID-19 goes further than the acute respiratory distress, thromboembolic events and deaths to a range of chronic sequelae that delay recovery and have a marked influence on daily functionality in large numbers of patients.

Lockdown days, monetary policies and travel restrictions severely affected the economic activities as well as the variations of major stock market indices. The rising number of COVID-19 and death cases also contributed to global inflation, unemployment and energy supply issues. In March 2020, the International Monetary Fund predicted a global recession that would be at least as bad as the 2007–2008 global financial crisis. Lockdowns or even less aggressive social distancing measures heavily impacted daily life and increased inequities, and had negative effects on educational outcomes, mental health and domestic violence.

Taken together, these factors had a significant impact on key stakeholders’ considerations regarding timelines for vaccine development and authorisation. For perhaps the first time, the global policymakers began understanding how antiviral vaccines are essential for not only public health, but also economic recovery, and even global security. Strong political engagements and a sense of global vulnerability and urgency, combined with risk–benefit assessments, led to high levels of financial investment and expedited review by regulatory agencies. Political will and global vulnerability also enabled a supportive context for partnerships and collaboration, with the necessity of openness to share research outputs, improve vaccine design, accelerate clinical development and expedite access.

**Unprecedented financial investment**

The *Lancet* Commission on lessons for the future from the COVID-19 pandemic provides details of the various expenditures. Globally, dozens of billions of dollars were invested in COVID-19 vaccine research and development (R&D) and advance purchase agreements (APAs) from the US Government Operation Warp Speed (an interagency programme including different departments, the Biomedical Advanced Research and Development Authority, and private firms), the World Bank and the Coalition for Epidemic Preparedness Innovations (CEPI). In China, it has been estimated that over $1 billion were invested in COVID-19 vaccine R&D, about half from public and half from private sources. These massive investments de-risked COVID-19 vaccine clinical development. By sharing financial burden and risk of failure among multiple stakeholders, APAs between governments and pharmaceutical companies provided a level of economic security for COVID-19 vaccine development. Investments were also made in manufacturing and key inputs such as vials and syringes to help improve success in the large challenge of scale-up.

**Massive demand**

The unprecedented high demand for COVID-19 vaccines by governments such as the US Government Operation Warp Speed and the COVID-19 Vaccines Global Access (COVAX) emerged in the absence of other pharmaceutical interventions. One of the reasons for massive demand is that many wealthy countries had placed advance orders and paid deposits for vaccine quantities far exceeding their needs. The necessity to regroup and coordinate funding to support vaccine development was accompanied by the emergence of global market for approved vaccines. By bringing together key stakeholders including governments, global health organisations, manufacturers, scientists, private sector, civil society and philanthropy, COVAX’s aim is to provide innovative, fair and equitable access to COVID-19 vaccines worldwide. The organisations focusing on emergencies, including the COVAX facility, by their early engagement and financing allowed much faster timelines for clinical development by lifting some of the initial hurdles faced by vaccine developers. The sheer volume of the demand aggregated by the COVAX facility provided incentive to allow clinical R&D at risk. Of note, the important role of the academic sector, for both preclinical work and...
clinical development, has also played a critical and cost-effective role.27

**Expedited regulatory review**

Regulatory authorities in countries of origin adopted a proactive approach to rapidly set minimum clinical, non-clinical and manufacturing data requirements that would enable EUA for rapid access of safe and effective vaccines. Early and iterative guidance consultations of manufacturers with regulators contributed to improving timelines. In order to allow more flexibility in the submissions and rolling reviews, regulators prioritised COVID-19 reviews over other health-related products. Through the European Medicines Agency’s rolling review process, COVID-19 vaccines could be approved in record times, ranging from 17 to 36 days.28

The WHO Emergency Use Listing Procedure (EUL) is a procedure for assessing and listing unlicensed vaccines to expedite their availability to people affected by a public health emergency. WHO EUL was a prerequisite to the deployment of vaccines through COVAX and for many countries by expediting their own regulatory approval to import and distribute COVID-19 vaccines.30

Of note, several vaccines were being used before WHO EUL. The Sinovac vaccine first acquired EUA in China in August 2020, soon followed by Indonesia, Turkey and Brazil. The China’s National Medical Products Administration granted conditional marketing authorisation in February 2021, followed 5 months later by WHO EUL. The Sinopharm-Beijing vaccine received EUA in the United Arab Emirates in September 2020, then full approval in early December, followed by conditional market authorisation in December 2020, and finally 5 months later WHO EUL in May 2021.23 Similarly, AstraZeneca’s COVID-19 vaccine has been granted EUA for UK use by the Medicines and Healthcare products Regulatory Agency in December 2020,31 was then granted EUA in India as well as Argentina, Dominican Republic, El Salvador, Mexico and Morocco for the active immunisation of adults in January 2021, before WHO EUL.32

**Building on past research investments**

Building on past research investments

Earlier fundamental and translational research to develop innovative vaccine platform technologies (eg, mRNA33–35 and non-replicating viral vectors36–39), along with R&D activities on other coronaviruses with pandemic or epidemic potential (eg, SARS-CoV-140 and MERS41) offered a fertile background to build upon. These were rapidly leveraged for COVID-19 vaccine development and provided vaccine developers with a better understanding of the SARS-CoV-2 biology, possible transmission mechanisms and virus target for inducing an adequate immune response. The spike protein was used in all mRNA and viral-vectorised and protein-based vaccines. This enabled a much faster development of COVID-19 vaccine candidates for preclinical and clinical testing. For some pathogens such as HIV, tuberculosis or malaria, the preferred protective antigens have not been clearly identified, whereas many outbreak pathogens are viruses that employ surface proteins for host entry and fusion. In the case of coronaviruses, years of research had shown how a unique spike protein as vaccine antigen would elicit a neutralising antibody response, which can block infection, as well as memory B cells and T cells.42

**Accelerated clinical testing**

The development of safe and efficacious COVID-19 vaccines occurred in 12 months rather than 5–10 years.10 A de-risked clinical development pathway with accelerated decision-making allowed consolidated clinical testing phases to be conducted in countries with high burden of SARS-CoV-2 and clinical sites with high-standard and adjustable research capacity and clinical trial infrastructure. Rapid response platforms were used to great effect: mRNA, viral-vectorised and whole inactivated virus vaccines have been developed and manufactured rapidly compared with other technologies, such as subunit and live attenuated vaccines, each requiring extensive manufacturing process development.

**LESSONS LEARNT AND CHALLENGES**

The COVID-19 pandemic illustrates that the traditional, often time-consuming, barriers to vaccine development and authorisation can effectively and efficiently be addressed, resulting in significantly faster development timelines. Indeed, CEPI called for vaccines to be ready for initial approval and mass manufacturing within 100 days of identifying the next pandemic pathogen.10 These lessons learnt should contribute to better preparation for a future pandemic as well as creating a more efficient framework for vaccine R&D, as well as regulatory approval mechanisms for epidemic and endemic diseases. Aspiring towards 100 days must come with global distributed manufacturing in the future including new technology such as mRNA.

Decades of scientific R&D paved the way to faster COVID-19 vaccine development. Structural biology research into antigen design as well as vaccine platform development and identification of immune correlates of protection should continue to be funded.

Moreover, while mRNA vaccines proved to be effective against COVID-19, so did multiple other vaccine approaches that included adenovirus and other viral vectors, as well as recombinant protein or nanoparticles. There is no way to predict an optimal vaccine technology for any given pathogen. Though while there is a need to build mRNA vaccine development capacity in low/middle-income countries (LMICs), this should not happen at the expense of other successful technologies, including, for example, the vesicular stomatitis virus approach that benefited the development of Ebola virus vaccines.

An early and continuous dialogue between regulators, vaccine developers, manufacturers and country
policymakers through the establishment of open regulatory forums remains key to discuss issues and to develop and disseminate guidance documents or roadmaps to build trust and contribute to regulatory harmonisation and reliance. This may however be hampered by a limited replicability in a non-pandemic situation where the sense of urgency and societal impact may be lacking. The prioritisation of COVID-19 interventions by regulators was however done to the detriment of other interventions for other diseases during the pandemic.43–45

Importantly, the recent surge of the Omicron variant of concern, with its multiple subvariants with immune escape capabilities,46 reminds us bitterly that the COVID-19 pandemic has not gone away and that the development of new improved and more broadly protective vaccines is urgently needed.47,48 This raises another issue that did not exist for the clinical development of first wave of COVID-19 vaccines. The first COVID-19 vaccines were tested for efficacy in stringent placebo-controlled studies in individuals who were not SARS-CoV-2 infected.49 The next strategy acceptable for regulators was to compare a new vaccine for immuno-bridging non-inferiority studies with an existing vaccine proven to be efficacious, still in unvaccinated and seronegative individuals.50 This was also challenged by the accessibility to a comparator COVID-19 vaccine (perceived as a competitor). The landscape has since dramatically and rapidly changed as most of the populations have now become SARS-CoV-2 seropositive because people are either vaccinated (>60%),51 or infected, or both (hybrid immunity). In the absence of correlates of protection widely accepted by regulators, newly developed vaccines would then have to be tested in SARS-CoV-2 seropositive individuals as a booster vaccine and assessed by immune responses against the variants of concerns. Vaccines designed to induce mucosal immune responses may be more effective in reducing virus transmission but will require further efficacy trials since the correlates of protection must be re-established for mucosal protection. Developers and regulators are engaged in in-depth discussion for new clinical trial designs and vaccine approvals.

While COVAX has undoubtedly made an important contribution to addressing global inequities in the spirit of solidarity by increasing access to COVID-19 vaccines, the model has shown its own limitations.52 COVAX was highly dependent on the goodwill of high-income countries to share part of their vaccines with COVAX instead of bilateral agreements. Advanced purchase mechanisms have exacerbated inequities. While de-risking and incentivising vaccine developers and manufacturers, it was also associated with risks for countries in purchasing the vaccines and paying more than needed.53 Creating a regulation framework of advance purchase mechanisms might mitigate these inequities.

The development of safe vaccines that meet the needs of LMICs represents an essential link to confidence in vaccines and its impact on demand. Vaccine-related safety concerns were raised following the description of adverse events of special interest (AESIs) in case series, health system surveillance studies and pharmaco- vigilance reports. Although remaining very rare events, these AESIs include vaccine-induced immune thrombocytopenia with cerebral venous sinus thrombosis,54 capillary leak syndrome,55 and myopericarditis56 57 to cite the most prominent ones. Such reports were generated mostly in high-income countries. Little is known about such events in LMICs as the number of vaccines administered was much lower than in high-income countries to detect such rare signals and the development of pharmaco-vigilance systems remains limited.9,58 The growing COVID-19 vaccine rollout requires robust pharmacovigilance systems and global coordination of post-licensure surveillance, in particular in LMICs.59

Worldwide, more than 13 billion vaccine doses have been administered as of 13 December 2022.60 In the post-pandemic period, demand, however, is currently declining. Although large numbers of doses are now available, demand may not keep up with supply, risking production of vaccines without a place to go. Further, this does not negate the need in LMICs to sort out future operational efforts required to get product from airports to arms in a more equitable manner should future emergencies happen. As vaccines are already available, the global community may need to turn to pull incentives for the longer term to incentivise innovation needed for LMICs and encourage continued focus to improve on existing vaccines.61 Sustaining the progress observed in reducing the health and economic costs of the pandemic will require continued development of vaccines effective against emerging variants, maintenance and expansion of the manufacturing capacity to produce large volumes of vaccines at scale as quickly as possible, and all necessary measures to make these vaccines accessible and affordable to those in need. Several economic factors support the need for a continued federal investment in COVID-19 vaccines. Although contributing to social benefits, manufacturers may be tempted to invest less in the future as they only benefit of a limited fraction of the global wealth generated. Government investments in development, manufacturing and procurement of vaccines to ensure affordable access were key to overcome such challenges and likely will remain essential in the future.24

CONCLUSIONS
The COVID-19 pandemic triggered a sense of vulnerability and urgency that led to concerted action by key stakeholders including governments, funders, regulators and industry to overcome traditional challenges for vaccine candidates for their development and to reach authorisation. CEPI, G7 and G20 have all adopted the ambition for 100 days to use of vaccines in a pandemic situation in the future.18 However, there remains urgency to meet these 100-day targets in ways that avoid the disastrous vaccine inequity situation that plagued the global COVID-19 response during the first 2 years of the
pandemic, and enabled the emergence of the delta and omicron variants in India and Africa, respectively.

The lessons of the SARS-CoV-2 pandemic may offer guidance to governments and funders to revisit the vaccine ecosystem to better protect populations from other pandemic, epidemic and endemic disease threats. Investments in infrastructures and training needed to improve success in R&D of vaccines for other infectious diseases should also remain a priority of equal importance to respond to regional demands and contribute to sustainability.

A new era of vaccinology has emerged from the rapid R&D of COVID-19 vaccines, with innovative platform technologies and an adaptive vaccine industry which should benefit all, in particular the most vulnerable populations. We must however stay humble and acknowledge that the unique circumstances that led to COVID-19 vaccines may not be universally applicable. If we are to imagine the future of vaccinology through the lens of COVID-19, we need to recognise that some of the conditions that made rapid COVID-19 vaccine development possible cannot and arguably should not be replicated.

Now is the time to take a longer-term view and ensure that investments are not just looking at the early winners, but as new vaccines are developed that there are incentives to build expertise in particular for manufacturing that can be leveraged for LMICs and other markets to ensure equity in innovation, access and delivery (further discussed in other papers in this issue).

The creation of vaccine manufacturing hubs such as the Partnership for African Vaccine Manufacturing, an initiative of the African Centers for Disease Control and Prevention and the African Union, is certainly the way of the future for African Vaccine Manufacturing. A new era of vaccinology has emerged from the rapid R&D of COVID-19 vaccines, with innovative platform technologies and an adaptive vaccine industry. The trillion dollar vaccine gap will benefit all, in particular the most vulnerable populations.

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Competing interests JLE is an employee of the International Vaccine Institute. He is chair of the Military HIV Research Program/Emerging Infectious Diseases Branch/Henry M Jackson Foundation Safety Monitoring Committee and member of the Benefit-Risk Assessment of Vaccines by Technology Working Group (BRAVOT) of the Brighton Collaboration. MS is employed by the Coalition for Epidemic Preparedness and Innovation (CEPI) and is a member of the Board of Trustees of the International Vaccine Institute. LP-D served on an advisory board for GSK. SG is an inventor of intellectual property licensed by Oxford University Innovation to Astrazeneca. PJH is a co-inventor of a COVID-19 recombinant protein vaccine technology owned by Baylor College of Medicine (BCM) that was recently licensed by BCM non-exclusively and with no patent restrictions to several companies committed to advance vaccines for low/middle-income countries. The co-inventors have no involvement in license negotiations conducted by BCM. DT is the director of Research and Content at the World Innovation Summit for Health, an initiative of Qatar Foundation. SA-K serves as special advisor (on pandemics) to the Director-General of the WHO. He is a commissioner of the African Union Commission on COVID-19. He has served in the past on the SANOFI medical advisory board for COVID-19 vaccines and as a commissioner of the Lancet Commission on COVID-19. JHK was a consultant for SK bioscience and is an unpaid consultant to the scientific advisory board of Everest.

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