Health policy 125 (2021) 553–567

Contents lists available at ScienceDirect

Health policy

journal homepage: www.elsevier.com/locate/healthpol

# COVID-19 vaccine challenges: What have we learned so far and what remains to be done?

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ARTICLE INFO

*Article history:*
Received 10 October 2020
Revised 17 March 2021
Accepted 23 March 2021

ABSTRACT

Developing and distributing a safe and effective SARS-CoV-2 (COVID-19) vaccine has garnered immense global interest. Less than a year after COVID-19 was declared a pandemic, several vaccine candidates had received emergency use authorization across a range of countries. Despite this scientific breakthrough, the journey from vaccine discovery to global herd immunity against COVID-19 continues to present significant policy challenges that require a collaborative, global response. We offer a framework for understanding remaining and new policy challenges for successful global vaccine campaigns against COVID-19 as well as potential solutions to address them. Decision-makers must be aware of these challenges and strategize solutions that can be implemented at scale. These include challenges around maintaining R&D incentives, running clinical trials, authorizations, post-market surveillance, manufacturing and supply, global dissemination, allocation, uptake, and clinical system adaption. Alongside these challenges, financial and ethical concerns must also be addressed.



## 1. Introduction

Immense global interest has risen around the development and distribution of safe and effective SARS-CoV-2 (COVID-19) vaccines. To date, multiple vaccine candidates have received authorizations for emergency use and many countries have initiated vaccination rollout efforts. Vaccines being developed, manufactured, and delivered in under a year is a notable scientific feat – enough so that Science Magazine named this the top breakthrough of 2020 [1]. However, from ensuring continued development of vaccine candidates, to authorizing, producing, distributing, administering, and monitoring existing ones, the COVID-19 vaccine process remains laden with policy challenges. While literature tends to explore these challenges in siloes, these issues are inherently overlapping and interdependent. As such, we offer a framework for understanding 11 of the remaining and new policy challenges related to COVID-19 vaccination efforts, and some potential solutions to address them.

The framework, as illustrated in Fig. 1, consists of three main 'D'-dimensions of achieving widespread global COVID-19 immunity via vaccinations. The three D's are 'development', 'dissemination', and 'deployment': ensuring the continued development of safe and effective vaccines, supplying and disseminating the vaccine around the world, and deploying the vaccine within countries. Under these dimensions, there are 11 challenges to achieving these goals: maintaining strong and sensible R&D incentives; running coordinated clinical trials; authorizing safe and effective vaccines efficiently and transparently; monitoring effectiveness during (and after) vaccine deployment; ensuring equitable vaccine access globally; manufacturing sufficient quantities and maintaining supply chain capacity; safely and securely transporting and delivering vaccines; determining fair vaccine allocation; encouraging the uptake of vaccines; ethical implications of vaccine passports and other vaccine requirements; and adapting clinical and health research systems. Financing decisions and ethical considerations will also need to be made from the start of vaccine R&D through to clinical system adapta-

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https://doi.org/10.1016/j.healthpol.2021.03.013

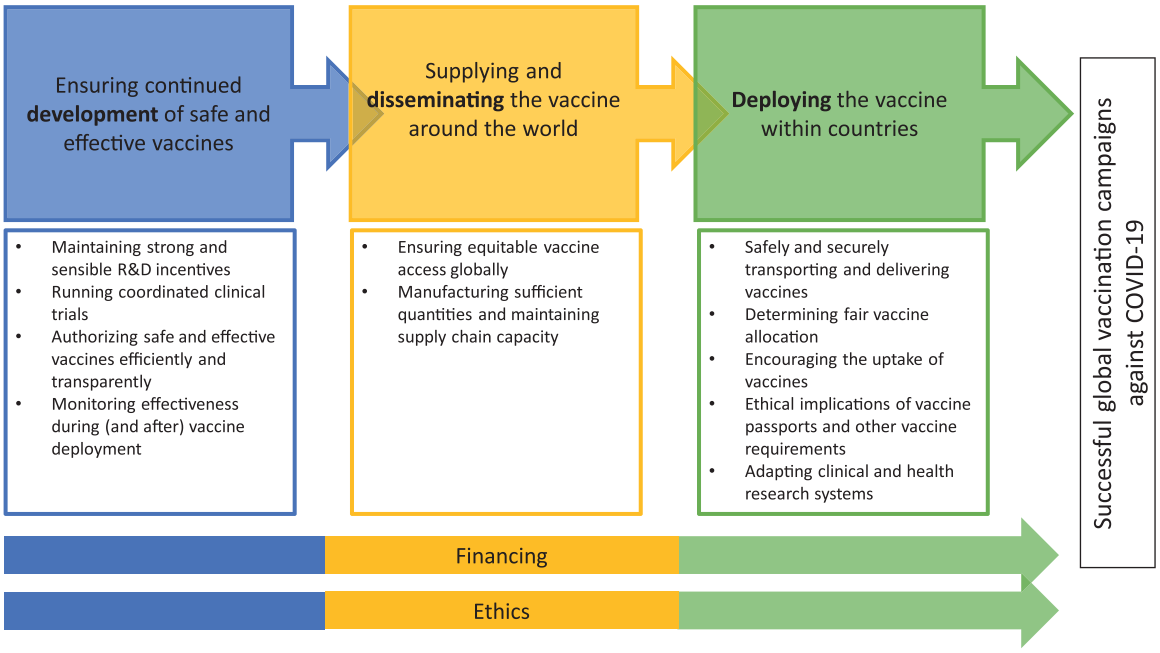


**Fig. 1.** A framework for understanding 11 remaining and new policy challenges in the implementation of successful COVID-19 vaccination campaigns.

tions. As such, these are represented as cross-cutting challenges in the framework.

## 2. Ensuring continued development of safe and effective vaccines

While several vaccines have recently gained (or are on the cusp of gaining) emergency use authorizations from countries around the world, the end of the pandemic is still a way off: many of the first generation vaccines require ultra-cold chain technology and are expensive, proving significant hurdles to global vaccination campaigns, and especially in low- and middle-income countries (LMICs); furthermore, we still do not know how long vaccines will remain effective in individuals over time; and the rise of new variants pose concern over mutations with high vaccine escape potential. As such, governments must continue to develop new vaccines and optimize their safety, effectiveness, and quality. We identified four primary challenges involved in achieving this: maintaining strong research and development incentives; running coordinated clinical trials; authorizing safe and effective vaccines efficiently and transparently; and continuing to monitor their impacts as (and after) they are deployed. Importantly, each of these challenges will require greater public engagement and intergovernmental cooperation and support in the redesign of incentives, institutions, and processes.

### *2.1. Maintaining strong and sensible R&D incentives*

In early December 2020, less than one year after the start of the pandemic, COVID-19 vaccines were already gaining authorizations in countries around the globe. This feat would not have been possible without the tremendous effort, collaboration, partnership, and financial support that went into the development of these products. However, even though a handful of vaccines are already being administered in countries around the world, more options on the market are necessary to vaccinate the billions and billions of people needed for herd immunity.

For these first-generation vaccines, governments used both push mechanisms (i.e. direct grants to companies) and pull mechanisms (i.e. Advanced Market Commitments) to stimulate R&D without ties to quality or efficacy of eventual vaccine products – an understandable short-term solution given the situation in 2020. However, COVID-19 is unlikely to disappear soon, and we must now consider longer-term efforts. We are nowhere near the vaccine administration levels needed for global herd immunity, new variants of concern are emerging [2], and we still do not know how long current vaccines remain effective and whether yearly or other periodic boosters are necessary. Incentive structures should undergo systemic changes so that manufacturers continue to search for viable candidates.

It is unlikely that all remaining and future vaccine candidates will meet efficacy thresholds for clinical trials. We have already seen the withdrawal of several candidates – even ones from major pharmaceutical developers [3]. Continued incentives are needed to maintain robust R&D efforts to ensure vaccine effectiveness, safety, and quality, and to generate second and third generation vaccines to meet the ever-changing needs of populations across the globe. With the emergence of new variants, there is also a rise in interest around the development of a “universal ‘variant-proof’ vaccine, able to fend off different varieties of the same virus family” [4]. The challenge of maintaining strong R&D incentives is bolstered by the nature of vaccine development, which presents higher costs and risk relative to other pharmaceuticals [5]. Governments and donors could consider implementing additional financing mechanisms to encourage R&D, including patent purchasing [6], patent pooling, and bonds [7]. The Options Market for Vaccines (OMV) model (based on the Options Market for Antibiotics model), where purchasers would make financial investments into COVID-19 vaccine R&D in exchange for reduced future prices, has been proposed as a potentially effective way to combine push and pull incentives for vaccine development in the current pandemic setting [[5,8–10]. CEPI has already received some political backing for its proposal to speed up the development time of new vaccines to 100 days; but it will need substantial international and financial support to reach this ambitious goal [11].

In late 2020, European Commission president Ursula von der Leyen announced that a European equivalent to the US Biomedical Advanced Research and Development Authority (BARDA) would be established in efforts to better prepare for future disease outbreaks – the European Health Emergency Preparedness and Response Authority (HERA) [12]. However, there are still few details on how HERA will be funded, governed, and if it will utilize innovative financing methods such as the OMV model described above to incentivize R&D and guarantee fair prices [13,14].

### 2.2. Running coordinated clinical trials

Another challenge in the COVID-19 vaccine process is that governments and developers must decide how to set the standards for valid clinical trials in humans at unprecedented speeds. Developers may also face tough decisions in determining whether they need to scrap or delay vaccine candidates for a disease that the world so desperately needs inoculations for. In December 2020, amidst news celebrating the start of vaccine administration in the US and the UK, the University of Queensland had to abandon the development of one candidate after trial participants were receiving false-positive HIV test results [15]. Sanofi and GSK also announced a delay to a vaccine candidate which was showing a good immune response in younger trial participants, but a low response in older patients [15]. Unless challenge trials – where study participants are intentionally exposed to the infectious disease organism in question – are being utilized (such as the one recently initiated in the UK [16]), phase III vaccine trials must be undertaken in settings where there is sufficiently high levels of infection risk so that an effect can be identified with a degree of confidence [17].

Methodological issues and communication errors in clinical trials can lead to unrepresentative data and can even fuel vaccine hesitancy. For example, some of the participants in the AstraZeneca/Oxford vaccine's UK-based clinical trial received roughly half of their intended first dose and additionally, the timing between first and second doses varied between study participants, leading to criticism of the company's initial 90% efficacy claim because these levels were seen in those who did not receive the standard regimen [18].

Additionally, within individual countries, clinical trials may not include adequate or representative sample sizes and demographics. Clinical trials in HICs—especially challenge trials—have historically included young, healthy participants with limited racial and ethnic diversity, posing a significant barrier to generalizability [19]. As the burden of COVID-19 falls particularly on older, co-morbid, and minority ethnic populations, it is essential that clinical trial participants are diverse and representative of those in the general population who will receive the vaccines when they successfully deliver to market. AstraZeneca faced additional backlash upon the discovery that in the clinical trial arm which reported 90% vaccine effectiveness (where patients received a half-dose for the first injection), the trial participants were all aged 55 and below [18]. Limited racial and ethnic diversity in clinical trials can also hinder trust in vaccines among minority populations further down the line. According to the London School of Hygiene and Tropical Medicine (LSHTM) COVID-19 vaccine tracker, more than 80% of the Pfizer/BioNTech Phase III clinical trial participants are White; 99% in the Gamaleya Phase III trial, 79% in Moderna's; and 83% in the Oxford/AstraZeneca Phase III trials [20]. When incentives are attached to trial participation, careful ethical considerations must be made to ensure that potential benefits to society outweigh the risk of harm imposed on trial participants—many of whom may be of lower socioeconomic status.

The WHO took a commendable step by proposing a Solidarity Vaccine Trial with an adaptive design (i.e., enabling participants to continually be added) and participants from multiple member states [21]. Pharmaceutical developers have also made unprecedented strides in transparency efforts by publishing protocols and data publicly [22]. However, there are still areas for improvement. Clinical trials for vaccines are often executed differently across different countries. To maximize statistical rigor, trials need broad consensus, standardized protocols and transparency requirements, a challenge given the variations in regulatory regimes across countries. The EU Clinical Trials Register was developed to do just that across European countries [23]. However, with recent announcements about HERA, questions remain as to how these institutes will coordinate and operate in practice [24]. Ultimately, governments and international agencies should play a role in determining the thresholds and protocols for trials, while private sector industry assists in financing the trials themselves.

### 2.3. Authorizing safe and effective vaccines efficiently and transparently

After the development of a viable vaccine, relevant health technology assessment bodies need to authorize the product for emergency use or grant market licensure. So far, the regulatory agency processes have been disappointingly disjointed, and have come out with different advice for the same vaccines and in different time frames. When reviewing 24 countries' processes, researchers identified more than 50 regulatory pathways to accelerated vaccine approval [25]. Experts have called for more harmony and suggested that broad agreement across regulators on definitions for different approval types could help pharmaceutical companies prepare drug applications more quickly and share and compare findings and analyses more easily – in turn improving regulatory efficiency and trust [26].

On 21 December, the European Medicines Agency (EMA) recommended the Pfizer/BioNTech vaccine for a conditional marketing authorization in the EU. By that point, the same vaccine had already received some form of authorization in 15 countries; including in the UK, US, and Canada [27]. Variation extends beyond regulatory approvals to differences in the conditions for accessing vaccines. Early on, the US [28] and the EU [29] accused the UK in being too quick to give the Pfizer/BioNTech vaccine the green light, claiming there was not enough data; however, weeks later the FDA and the EMA had also granted emergency use authorizations for the same product, including for pregnant women. Meanwhile, the UK still advises against COVID-19 inoculations in pregnant women unless they are considered high risk because of other health conditions or occupation. The AstraZeneca/Oxford vaccine was recommended for use in all adults when it first received authorization in the UK. By contrast, several European countries implemented restrictions against use of this vaccine in older people when they first issued authorizations [30].

Beyond the variations in regulatory process length and the recommendations made, the actual processes themselves vary. Some regulatory bodies, such as the FDA, use open forums to deliberate and draw on their own statistical analyses based on raw data from clinical trials, while others do not [26]. Several countries have authorized vaccines without third stage trial data. For example, in the summer of 2020, the Russian Federation approved a vaccine for use while it was still in the first phase of testing and did not have any results [31]; China authorized several vaccines for emergency use with only phase I and II trial data [32]; and in late 2020, India approved emergency use of Covaxin while it was still undergoing phase III testing [33].

Many regulatory bodies have released plans for fast-tracking vaccines which have been modified to respond to new COVID-19 variants, but these also differ. FDA guidance for modified COVID-19 vaccines requires two non-inferiority studies, one which shows immunogenicity in previously unvaccinated, uninfected participants,

and the other which shows immunogenicity in those who have received the vaccine before [34]. The EMA guidance also expects this, but additionally requires several other endpoints be met; for example, the lower bound of the 95% confidence interval in seroconversion rates for the variant compared to the parent strain cannot exceed −10%, and seroconversion rates must be at least four times in titer from pre- to post-vaccination [35].

This variation across licensing processes, data requirements, and outcomes can prove problematic – mitigating confidence and trust around the safety and effectiveness of vaccines, delaying successful inoculation campaigns, and more. Millions of doses of the AstraZeneca vaccine are piling up unused in Europe after the discrepancies in initial advice for use in older adults mentioned above have fueled doubts around the vaccine [30]; contributing to further slowdowns in the EU COVID-19 vaccination rollout. Thus, efforts should be made to increase coordination and transparency across regulatory agencies.

There has already been some progress in this area: researchers highlight that in 2012, the WHO established the International Coalition of Medicines Regulatory Authorities (ICMRA) so that regulators could share information and approaches [26,36]. The ICMRA, now consisting of 29 countries, has a working group focused on coordinating COVID-19 vaccine monitoring efforts across countries. But despite several ICMRA meetings held and statements released since April 2020 focused on aligning regulatory processes [37], the uncoordinated efforts described above have still arisen, signaling that further progress can be made. Pathways by which regulators can exchange information "in the same units and about the same end points, and to make decisions based on the same data" at similar speeds in a transparent and open fashion still need to be developed and agreed upon [26,36].

### *2.4. Monitoring effectiveness during (and after) vaccine deployment in the general population*

Adequate post-marketing surveillance systems can help promote continued confidence and uptake in vaccines. Governments need mechanisms to closely monitor and evaluate data on effectiveness and adverse events as vaccinations are introduced to a population. Once again, transparency and coordination of these processes are also required for success. It is key to determine what metrics are most useful to measure and monitor a vaccine's quality and effectiveness (e.g., transmission rates, case fatality, adverse effects) and outline how these data can be reported in real-time to other nations. Efforts in monitoring COVID-19 vaccines have begun in some countries [38], but beyond these individual initiatives, an international body, such as the WHO, could be charged with going further and standardizing protocols for efforts to monitor the safety and effectiveness of vaccines as they are administered around the world. Current evidence suggests that the authorized COVID-19 vaccines are very safe, and the risk of harmful side effects is low [39]. Still, it is important to continue to form consortiums to monitor the safety and effectiveness of these products so that improvements can be made to future vaccines and programs. Real-world evaluations of immunizations which discern the vaccine's impact alone from that in combination with nonpharmaceutical interventions (NPIs) such as shelter-in-place orders or social distancing could also be conducted.

## 3. Supplying the vaccine around the world

As more vaccines are developed and authorized for emergency use, governments should prepare for the mass production and distribution of the billions of doses that are required around the globe, and can implement innovative solutions to scale up manufacturing capacity. Already, we have seen supply chain disruptions, failures to meet expected delivery quantities and timelines [40], and immense global disparities [41] in vaccine access with some even terming it a 'vaccine apartheid' [42]. Supplying and delivering these vaccines around the world involves two key components: ensuring equitable vaccine access globally; and manufacturing sufficient quantities and maintaining supply chain capacity.

### *3.1. Ensuring equitable vaccine access globally*

Before distribution occurs, tools and procedural government mechanisms are needed to determine how many doses each country will secure and at what cost. This has become one of the most politically-driven challenges in this paper. Unfortunately, issues such as "vaccine nationalism," or refusal to distribute vaccines across national borders, is preventing sufficient supply of vaccines globally. Many HICs have pursued their own agreements with pharmaceutical companies for COVID-19 vaccines. These individual, siloed deals do not typically lead to the best global procurement practices, and instead we have seen wealthier countries securing as many vaccine doses as possible; even when it hinders vaccine accessibility elsewhere. Several HICs have purchased enough doses to vaccinate their populations several times over: Canada, for example, could fully vaccinate its population five times over (585% possible vaccination coverage) in the (admittedly unlikely) event that all the vaccines for which it has purchased doses are authorized for use [43]. Meanwhile, the total potential population that can be vaccinated in LMICs (including upper middle-income countries) is significantly smaller. According to the Duke Global Innovation Center, outside of COVAX agreements, China has purchased enough potential vaccines to cover 4% of its population, Algeria's and Syria's coverage is listed at 0%, and the African Union has purchasing agreements for potential vaccines to cover 40% of its population [41]. Some countries have even implemented export bans on vaccines [44].

In late-January 2021, approximately 40 million doses of the vaccine had been administered in at least 49 high-income countries, but just 25 doses had been given in one of the lowest-income countries [45]. The economic ramifications of these access disparities are significant. A study commissioned by the ICC Research Foundation suggests that if LMICs continue to have inadequate access to COVID-19 vaccines, global economic losses could accumulate to between $1.2–9.2 trillion, and more than half of this could fall on HICs [46]. Beyond the moral and economic arguments for global vaccine equity, there is also the scientific argument: leaving much of the global population unvaccinated could increase the incidence of new variants; and the more variants that arise, the more likely it is that one will have high vaccine escape potential [47]. The continued emergence of new variants with high vaccine escape potential would not just have negative implications for health and wellbeing of populations, but it would create further economic consequences and set off a cycle of revaccination/booster campaigns.

The COVAX facility was established with the goal of accelerating COVID-19 vaccine development and manufacturing and to ensure equitable access to these immunizations for all countries. Co-led by CEPI, Gavi, and the WHO, COVAX is the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator. COVAX aims to secure at least two billion COVID-19 vaccine doses by the end of 2021, with more than 60% of those going to 92 low-income countries [48]. By late February, COVAX had secured $6.3 billion [49] and delivered its first doses to Africa, so it is certainly making progress towards its goals [50]. However, when considering the trillions of dollars HIC governments are putting into stimulus packages alone, it becomes evident that further financial investments into COVAX can and should be made.

It has also been highlighted that small middle-income countries could become the "missing middle" as they face many disadvantages in purchasing and obtaining the vaccine. These countries often have low production capacity, may not be the first to benefit from the COVAX Initiative, and may lack the capacity to signal demand internationally [51]. A question, then, is how governments can be incentivized to coordinate efforts and design a "distributive manufacturing model" to purchase vaccines synergistically? One method may be for international agencies to subsidize countries with low population sizes but high manufacturing capabilities, so they can drive manufacturing efforts for countries with greater demand.

Several HICs have committed to donating some of their excess vaccine doses to LMICs – however, most are waiting until significant portions of their own populations are offered jabs before passing them across borders. Previous experience show that international vaccine donations involve many political, regulatory, indemnification, and liability complexities; experts suggest that plans should be established for COVID-19 donation processes sooner rather than later so that no country is caught off guard [52].

Pricing of the COVID-19 vaccines has also come into question. Reports suggest there is wide variation in price across different countries, with poorer, smaller countries and those with lower purchasing power paying the most [53,54]. For example, Saudi Arabia, Uganda, and South Africa are paying more than $5 per dose for the Oxford/AstraZeneca vaccine, and the European Commission is paying $3.50 per dose [54]. The company, which has committed to selling the vaccine without profit during the pandemic period, suggests that these price differences reflect differences in manufacturing factors. However, large price differentials exist for several of the other vaccines, and questions have been raised as to whether these are always justified, especially for vaccines that have been heavily subsidized by governments. Innovative financing R&D models which link a product's price to the initial investments and risks taken by a purchaser as well as the value of that product, such as the OMV model, could help us move to fairer and more sustainable pricing. This will become increasingly important if regular COVID-19 vaccination/booster campaigns are necessary to address new virus variants or waning vaccine efficacy over time, such as is the case with the seasonal flu.

### *3.2. Manufacturing sufficient quantities and maintaining supply chain capacity*

Because of the unprecedented demand for a COVID-19 vaccine, manufacturing capacity must be scaled in parallel with efforts towards vaccine discovery. This winter, the EU faced serious supply shortages, and political pressure on leaders mounted [55]. The supply challenges are even greater in many LMICs. Manufacturing capacity and supply chains should be strengthened, and quickly. At current rates, billions of people around the world might not have access to their first vaccinations until 2023 or 2024 [56].

Experts suggest that added capacity for three billion vaccines annually could have a global benefit of $17.4 trillion [57]. Some early investments in manufacturing capabilities for vaccines were made while clinical trials were still underway. This has been very important as it has enabled vaccine production to begin without delay as soon as the products are authorized. However, HICs have signed the majority of bilateral deals for these first-generation vaccines, and thus these early production capacity investments are largely benefiting wealthier countries at present. At the start of 2021, the People's Vaccine Alliance estimated that all of Moderna's expected vaccine production for 2021 and 96% of Pfizer's was already reserved by rich nations [45]. However, it is not too late to make further investments in manufacturing capacity that can benefit LMICs: recent models constructed by Castillo et al. suggest that "Even assuming a lag of several months…Adding capacity for 1 billion annual courses to the baseline 3 billion would avert $576 billion in comprehensive losses if the capacity comes only in July and $989 billion if the capacity comes online in April…and would speed up completion of widespread vaccination by over 4 months" [57].

Exchanges of intellectual property or technical know-how are likely to be controversial in the profit-making pharmaceutical industry; but these may be essential to scale up manufacturing capacity. One of the least controversial methods for this (perhaps) is a technology transfer whereby the original pharmaceutical product developer agrees to let another company manufacture its vaccine. Under normal circumstances, these partnerships are highly uncommon, but to-date several companies have already agreed to manufacture COVID-19 vaccines from other pharmaceutical developers which have successfully attained emergency use authorizations (or are on the cusp of doing so) [58]. Other proposals have been made which suggest governments should be able to jointly purchase patent rights for COVID-19 vaccines so that developers are rewarded for their innovative efforts and incentivized to engage in future work, while simultaneously, countries can manufacture and distribute doses to their populations [59]. Alternative suggestions include the introduction of contractual provisions on installing new capacity for vaccine buyers and the soliciting of bids [57]. Furthermore, an increasing number of countries are calling for compulsory licensing of COVID-19 vaccine patents so that they can manufacture and supply these products domestically [60]. However, some experts highlight that if intellectual property rights were removed this could open concerns around quality control (which could in turn increase vaccine hesitancy), and also suggest that even if intellectual property barriers were removed, many countries still will not be able to produce them without proper knowledge transfer from originators [61].

Alongside the manufacturing of the vaccines themselves, other related equipment must also be produced. Vaccines requiring cold-chain supply or other complex supply chain systems, present added challenges for countries without adequate existing infrastructure. And this will be even more difficult in countries with disruptions to supply chains because of conflict or natural disasters. About 20% of the world's poorest countries do not have adequate cold chain capacity [62], and while some countries do have equipment, in many instances it is old or broken and unable to keep vaccines cool. In late-June, the Gavi Board agreed to investigate how its Cold Chain Equipment Optimization Program (CCEOP) could be expanded to grow cold chain capacity in LMICs to meet COVID-19 vaccine demand [63].

Global shortages of and competition for glass vials and syringes may also serve as bottlenecks for large-scale immunizations [64]. Beyond export bans on COVID-19 vaccines themselves, those on materials like bags and filters, can lead to shortages of medical products all over the world because today's supply chains are so interdependent and global; and these can have impacts on health areas outside of COVID-19 [65]. Various stakeholders should contribute to planning and building supply chain resiliency amongst countries lacking infrastructure. Countries must also acknowledge that supply chains are global, and a disruption anywhere will impact necessary vaccine campaigns everywhere. Most manufacturing efforts thus far have been made by private sector investors, suggesting an opportunity for governments and international agencies to play a larger role in incentivizing manufacturing. One fiscally sustainable way to achieve this might be for governments to purchase equity in the production of vaccines or share some of the eventual profits of successfully approved vaccines. Governments and international agencies may also consider insurance mechanisms for pharmaceutical companies that indemnify losses in the case of failed marketing authorizations in exchange for early development of manufacturing facilities.

**Table 1**
Overview of current phase II/III, III, and IV COVID-19 vaccine candidates (as of 5 March 2021).

| NAME | DEVELOPERS[A] | PHASE[A] | MECHANISM OF ACTION[B] | TRIAL DESIGN[C] | PRIMARY OUTCOMES[D] | TOTAL PARTICIPANTS REGISTERED IN TRIALS, N[B] | PRIMARY COMPLETION DATE[C] | MANUFACTURE PROJECTIONS, 2021[B] | PART OF COVAX PROFILE[E] | STORAGE TEMP REQUIREMENTS[B] | IN USE?[B] | COUNTRIES REPORTING USE[B] | ONE VACCINE ACCESS TEST SCORE (OUT OF 20)[F] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AG0302-COVID19 | Anges, Takara Bio, Osaka University | 2/3 | DNA based vaccine | Double-blind | Adverse Events, Immunogenicity | 530 | May-21 | Pending | No | Pending | No | – | N/A |
| ZF2001 | Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences | 3 | Protein subunit | Double-blind | Efficacy, Safety | 30,216 | Apr-22 | Pending | No | Pending; 2 to 8°C is typical for protein subunit vaccines | No | – | N/A |
| AZD1222 | AstraZeneca + University of Oxford | 4 | Viral vector (Non-replicating) | Double-blind | Efficacy, Safety, Tolerability, Reactogenicity | 58,166 | Mar-21 | 3 billion | Yes | 2 to 8°C | Yes | Early/Emergency Use in numerous countries incl. UK, EU, India, Argentina, Dominican Republic, and El Salvador | 7 |
| COVAXIN/BBV152 | Bharat Biotech International Limited | 3 | Inactivated virus | Double-blind | Efficacy | 26,679 | Mar-21 | Up to 700 million doses | No | 2 to 8°C | Yes | Emergency Use in India | N/A |
| Ad5-nCoV | CanSino Biological Inc./Beijing Institute of Biotechnology | 3 | Viral vector (Non-replicating) | Double-blind | Efficacy, Safety | 42,382 | Dec-21 | Pending | No | Pending; 2 to 8°C or -15 to 25°C is typical for vectored vaccines | Yes | Full/Emergency Use in China, Mexico, and Pakistan | N/A |
| SCB-2019 | Clover Biopharmaceuticals Inc., GSK, Dynavax | 2/3 | Protein subunit | Double-blind | Efficacy, Safety | 22,150 | Jul-22 | Up to 1 billion doses | No | 2 to 8°C | No | – | N/A |
| UB-612 | COVAXX, United Biomedical Inc. | 2/3 | Protein subunit | Double-blind | Efficacy, Safety, Immunogenicity | 7,380 | Mar-23 | Up to 1 billion doses | No | 2 to 8°C | No | – | N/A |
| CVnCoV | CureVac AG | 3 | RNA based vaccine | Observer-blind | Efficacy, Safety | 40,674 | Mar-21 | 300 million | No | 2 to 8°C | No | – | 2 |

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**Table 1** (*continued*)

| NAME | DEVELOPERS[A] | PHASE[A] | MECHANISM OF ACTION[B] | TRIAL DESIGN[C] | PRIMARY OUTCOMES[D] | TOTAL PARTICIPANTS REGISTERED IN TRIALS, N[B] | PRIMARY COMPLETION DATE[C] | MANUFACTURE PROJECTIONS, 2021[B] | PART OF COVAX PROFILE[E] | STORAGE TEMP REQUIREMENTS[B] | IN USE?[B] | COUNTRIES REPORTING USE[B] | ONE VACCINE ACCESS TEST SCORE (OUT OF 20)[F] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sputnik V/Gam-COVID-Vac | Gamaleya Research Institute; Health Ministry of the Russian Federation | 3 | Viral vector (Non-replicating) | Double-blind | Efficacy | 44,754 | May-21 | Up to 1 billion doses | No | Lyophilised formulation requires 2 to 8°C; frozen formulation requires -18°C | Yes | Early/Emergency Use in numerous countries incl. Russia, Belarus, Argentina, Serbia, and Algeria | 0 |
| INO-4800 | Inovio Pharmaceuticals, International Vaccine Institution, Advaccine (Suzhou) Biopharmaceutical Co., Ltd | 2/3 | DNA based vaccine | Double-blind, dose-ranging | Efficacy | 1,321 | Sep-22 | >100 million doses | No | Room Temp | No | – | N/A |
| CAMS VACCINE | Institute of Medical Biology + Chinese Academy of Medical Sciences | 3 | Inactivated virus | Double-blind | Efficacy, Safety | 35,433 | Sep-21 | Pending | No | Pending; 2 to 8°C typical for inactivated vaccines | No | – | N/A |
| AD26.COV2.S | Janssen Pharmaceutical (Johnson & Johnson) | 3 | Viral vector (Non-replicating) | Double-blind | Efficacy | 77,034 | Jan-21 | 1 billion | Yes | 2 to 8°C | Yes | Early/Emergency Use in South Africa, Bahrain, and USA | 6 |
| COVLP | Medicago | 2/3 | Virus-like particle | Observer-blind | Safety, Efficacy | 32,016 | Dec-21 | 80 million doses | No | 2 to 8°C | No | – | N/A |
| mRNA-1273 | Moderna + National Institute of Allergy and Infectious Diseases (NIAID) | 4 | RNA based vaccine | Observer-blind | Efficacy, Safety | 34,320 | Oct-22 | Up to 1 billion | No | 2 to 8°C for up to 30 days; -15 to 25°C for long-term storage | Yes | Full/Emergency Use in numerous countries, including USA, Canada, EU, UK, and Israel | 2 |

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**Table 1** (*continued*)

| NAME | DEVELOPERS[A] | PHASE[A] | MECHANISM OF ACTION[B] | TRIAL DESIGN[C] | PRIMARY OUTCOMES[D] | TOTAL PARTICIPANTS REGISTERED IN TRIALS, N[B] | PRIMARY COMPLETION DATE[C] | MANUFACTURE PROJECTIONS, 2021[B] | PART OF COVAX PROFILE[E] | STORAGE TEMP REQUIREMENTS[B] | IN USE?[B] | COUNTRIES REPORTING USE[B] | ONE VACCINE ACCESS TEST SCORE (OUT OF 20)[F] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NVX-COV2373 | Novavax | 3 | Protein subunit | Observer-blind | Efficacy | 50,819 | Mar-21 | 2 billion | Yes | 2 to 8°C | No | – | 7 |
| BNT162 B1/B2 | Pfizer/BioNTech + Fosun Pharma | 4 | RNA based vaccine | Observer-blind, dose-ranging | Safety, Tolerability, Efficacy | 51,358 | Aug-21 | Up to 2 billion | Yes | -60 to -80°C | Yes | Full/Emergency use in numerous countries; granted emergency use approval by WHO on 31 Dec 2020 | Pfizer: 3 BioNTech: 3 |
| QAZCOVID-IN | Research Institute for Biological Safety Problems, Rep of Kazakhstan | 3 | Inactivated virus | Single-blind | Efficacy, Immuno-genicity | 3,244 | Mar-21 | Pending | No | Pending; 2 to 8°C typical for inactivated vaccines | No | – | N/A |
| BBIBP-CorV | Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products | 3 | Inactivated virus | Double-blind | Efficacy | 56,128 | Dec-21 | Up to 1 billion | No | 2 to 8°C | Yes | Full/Emergency use in numerous countries, including China, UAE, Bahrain, Egypt, and Hungary | N/A |
| WUHAN/ SINOPHARM VACCINE | Sinopharm + China National Biotec Group Co + Wuhan Institute of Biological Products | 3 | Inactivated virus | Double-blind | Efficacy | 52,864 | Mar-21 | Up to 600 million | No | Pending; 2 to 8°C typical for inactivated vaccines | Yes | Limited use in China and UAE | N/A |
| CoronaVac | Sinovac Research and Development Co., Ltd | 4 | Inactivated virus | Stepped-wedge clusters | Efficacy | 35,633 | May-21 | Up to 1 billion | No | Pending; 2 to 8°C typical for inactivated vaccines | Yes | Full/Emergency use in numerous countries including China, Azerbaijan, Brazil, Chile, and Colombia | N/A |

Sources:.

[A]The 5 March 2021 WHO COVID-19 Vaccine Landscape Tracker was consulted to identify COVID-19 vaccine candidates in phase II/III, III, and IV trials. One candidate, Zydus Cadila's ZyCoV-D was excluded from this list because only Phase I/II data could be found in the public domain. [B]Information on Mechanism of Action, Total Participants Registered, Manufacture Projections, Storage Temp Requirements, whether it was In Use, and Countries Reporting Use was extracted from the LSHTM COVID-19 Vaccine Tracker (last updated 15 March 2021). [C]Trial Design and Primary Completion Date Information were also derived from the LSHTM COVID-19 Vaccine Tracker, but for the latest and largest trial only (last updated 15 March 2021). [D]Primary outcomes were identified from publicly available clinical trial information listed on ClinicalTrials.gov (last updated 15 March 2021). [E]COVAX profile inclusion information came from two separate announcements issued by the agency in 2020 and 2021. [F]ONE Vaccine Access Test scores came from the March 2021 ONE Vaccine Access Test 2.0 Report. Further details and references for Table 1 can be found in supplementary file 1.

## 4. Deploying the vaccine within countries

After a government secures an appropriate supply of vaccines, it must take a whole systems approach to ensure fairness and equitability. This goal presents five primary challenges: safely and securely transporting and delivering vaccines, determining fair vaccine allocation, encouraging the uptake of vaccines, ethical implications of vaccine passports and other vaccine requirements, and adapting clinical systems.

### *4.1. Safely and securely transporting and delivering the vaccine*

An important element in the COVID-19 vaccine deployment process which has not received widespread attention to-date is security [66]. From the factory all the way to the patient's shoulders they were meant for, vaccines must be protected against theft and tampering. At the end of 2020, Interpol issued a global alert that criminal activity aimed at infiltrating and disrupting supply chains and spreading misinformation about fake cures via fake websites was likely to arise [67]. COVID-19 vaccines of unknown origin and authenticity have been listed on the black market for over $200 per dose [68]. In response to these threats, freight companies have ramped up security efforts to minimize risks of COVID-19 vaccine cargo tampering; they are selecting experienced drivers and conducting enhanced background checks, utilizing remotely operated digital locks, installing loud alarm systems, ensuring that vial pallets are unmarked, closely tracking shipments, and even holding training on responding to vaccine cargo attacks for drivers [68]. Not only do security systems need to stop cargo from being stolen, but they also must prevent any disruption to the supply chain that could threaten the integrity of the cargo. Governments must continue to ensure security efforts are upheld where they have already been initiated, and implement plans and protocols in places where they have not.

### *4.2. Determining fair vaccine allocation*

Since few countries have enough vaccines at hand to offer inoculations to their entire adult populations, governments are faced with the tough task of determining and defining priority groups for vaccination. As many have pointed out, "unequal access and vaccine availability risks exacerbating health inequalities," [69] so these decisions are not to be taken lightly. Across most countries, older adults and frontline health and social care workers are high on prioritization guidance lists. For example, the first three groups to be offered the vaccine in the UK were 1) residents in a care home for older adults and staff working in care homes for older adults; 2) all those 80 years of age and over and frontline health and social care workers; and 3) all those 75 years of age or older [70]. This is similar to the recommendations released by the CDC Federal Advisory Committee on Immunization Practices on 1 December 2020 to vaccinate healthcare workers and long-term care facility residents and workers in the first (1a) stage (although decisions are ultimately made at the state level) [71]. COVAX lists healthcare workers, older adults, and people with serious chronic conditions as target populations for the first stage of its vaccine deployment [72]. However, there are still differences: for example, the UK's Joint Committee on Vaccination and immunization (JCVI) has stuck to a strict age-based prioritization scheme, while the CDC and the WHO have occupational group-based prioritization guidance.

Even with these prioritization groups outlined at the national level, allocation decisions ultimately are dependent on the needs, risks and wants of a given population; the resources available (cold chain supply, personnel to administer it); and the logistics involved. For example, all doses of the Pfizer/BioNTech and Moderna vaccines must be used (or disposed of) within six-hours once a vial is opened. In many instances, this has led to healthy young individuals – who are far from reaching their spots in eligibility queues – receiving jabs that would have otherwise gone into the waste bin [73]. Even when considering one priority group, such as frontline healthcare workers, important decisions need to be made: for example, whether one healthcare facility should receive jabs before another or if older workers in a facility should be vaccinated before younger ones, etc. [74]. Additionally, it is important to consider equity across and within priority groups (i.e., to account for existing ethnic and socioeconomic disparities in any scheme and prioritize groups that are historically underserved) [75,76]. Furthermore, mechanisms need to be established to capture groups that may otherwise be missed within prioritization schemes, including undocumented migrants or homeless individuals.

### *4.3. Encouraging the uptake of vaccines*

Prior to licensure, COVID-19 vaccines should endure rigorous testing and procedures and information about these tests should be transparent and accessible to reassure the public about safety and efficacy. Otherwise, things such as the above-mentioned differences in regulatory advice and requirements can lead to suspicions and doubt around immunizations.

Numerous surveys show that significant portions of populations would refuse or are uncertain they would receive a COVID-19 vaccine if it were available to them/their children [77–80]. In part, this may be driven by conspiracies, misinformation, and a growing anti-vax movement. However, it is important to acknowledge that vaccine hesitancy is different from anti-vax sentiment and can be driven by both rational and irrational reasoning. In the age of social media and online information, fake news and misreporting on the safety of vaccines can spread rapidly, creating an 'infodemic' and increasing both anti-vax movements and vaccine hesitancy [81]. Throughout the pandemic, we have seen a slew of misinformation spreading from political leaders and celebrities, which is also fueling the infodemic fire [82]. To try to combat this, social media companies are attempting to fact-check and demote disinforming posts on their platforms [83]. However, reports highlight that these efforts have not been entirely successful and disinformation is still spreading [84]. Now that vaccines are becoming more widely available, policymakers and the scientific community can increase public trust through clear communication in order to squash anti-vax misinformation [69,85]. Partnerships between social media companies and influencers, governments, and international organizations can increase the amount of informative, fact-based content around the safety and effectiveness of vaccines.

COVID-19 vaccine hesitancy is particularly prevalent amongst marginalized groups who have been worst impacted by the pandemic. Surveys in the UK [86], US [87], and many other countries have shown that respondents from Black, Asian, and minority ethnic (BAME) backgrounds are less likely to accept the vaccine compared to White counterparts. Some of this hesitancy and distrust of the medical profession more broadly is likely grounded in a long history of structurally racist systems which have led to health inequalities and injustices. Furthermore, individuals from BAME backgrounds make up a disproportionate amount of low-paid, shift-working, frontline workers, so access barriers and inconveniences in attending jab appointments may also contribute to lack of vaccine uptake. To address this, vaccination appointments should be available at flexible times outside of traditional work hours [88]. Additionally, it must be acknowledged that vaccine rollout strategies are not one-size-fit-all; they should be sensitive to the contexts of local communities, and inclusive of local community leaders (religious leaders, etc.) to engender trust and higher vaccine acceptance [88–90]. Science plus approaches, where

there is engagement and dialog with vaccine hesitant individuals and communities to better understand and address their concerns around vaccines can be successful in improving uptake [91,92].

"First-mover" effect, or hesitancy caused by presumed risks associated with the first vaccines, may also discourage uptake by persons who normally receive immunizations [93]. Though false, many worry that corners have been cut in terms of safety because of the unprecedented speeds at which the first COVID-19 vaccines were developed. It is vital that any vaccine that comes to market has been thoroughly tested and held to high safety standards to build public confidence; and if any issues do arise, regulators should react quickly. For example, British authorities quickly issued recommendations against the use of the Pfizer/BioNTech vaccine in individuals with a history of serious allergies after two severe allergic reactions were observed in the first weeks of the vaccine's deployment in the US and the UK [94]. Once further data was collected, the agency determined that individuals with a history of anaphylaxis could be vaccinated, after all, and vaccine guidance was updated accordingly [39].

Furthermore, interventions to overcome vaccine hesitancy must be evidence-based. Some studies have demonstrated that interventions which facilitate vaccination directly (e.g., reminders, mandates) are more effective than those that seek to change what people think and feel (e.g., education campaigns, motivational interviewing) [95]. While it may be constitutionally or politically impossible for some countries to impose national vaccine mandates, there may be other influences (e.g. vaccine passports for travel) that make vaccination a de facto requirement in everyday life (discussed in further detail below). For those who remain unconvinced even with private-sector vaccine requirements, they may be swayed by celebrity vaccination campaigns [96] or by the introduction of 'opt out' policies where the default is to vaccinate [97].

### *4.4. Ethical implications of vaccine passports and other vaccine requirements*

Ethical considerations must be made at every step of the vaccine development, distribution, and deployment processes; however, debates have particularly grown around the potential implementation of vaccine mandates and vaccine passports. Private companies may require evidence of prior COVID-19 vaccination before customers can use their services [98]. For example, Qantas has announced that in the future, their travelers will need to prove that they have been vaccinated against COVID-19 before boarding international flights [99]. Countries such as Greece and Israel are also firming plans to launch vaccine passports [100]. Furthermore, some employers are considering policies which would require all newly hired staff to have the jab [101]. This has opened a slew of ethical questions and the weighing of benefits to society vs. those for the individual. Of course, we need populations to be widely vaccinated to return to 'normal' life and make up for over a year of losses due to halts in economic activity, travel, education, etc. However, vaccine requirements could pit those who are further down in the vaccination queue against those who are already inoculated: those from poor countries against richer ones; younger, healthier people against older, multi-morbid ones; pregnant women and mothers and individuals from minority ethnic backgrounds, against their male/White counterparts. Vaccine passports for travel may also require interoperable digital data systems, which will create further complexities around international law and trust. Governments should seriously consider all the ethical dimensions when making decisions around vaccine mandates or passports for travel, employment, and beyond. If vaccine passports or requirements are indeed implemented, there should also be stipulations for individuals who cannot be immunized for various reasons (immunocompromised, pregnant, etc.).

Currently, no vaccine is authorized for use in children. But if this changes, even more ethical challenges will arise. For example, it remains to be seen whether schools will require children to be vaccinated to attend as a mechanism to protect fellow students, teachers, and the school communities at large. Additionally, if vaccine passports are implemented, it remains unclear whether there will be exemptions for children, or whether this would mean that they (and their accompanying parents/guardians) will be unable to travel unless regulatory authorizations change. Vaccine hesitancy is already an issue in the adult population, but it may prove even stronger for adults making decisions about vaccinating their children, especially considering that the side effects of the jabs (fever, lethargy, etc.) may be more severe than COVID-19 infection in children (on average). Without vaccinating children, who make up about 30% of the global population, against COVID-19, it is unlikely that we can achieve global herd immunity to the illness via a vaccine. Thus, ethical considerations on the value of global herd immunity and protecting the greater good must be made alongside those on the value of the freedom of choice in healthcare decision-making.

### *4.5. Adapting clinical and health research systems*

Not only will governments need to vaccinate as much of their populations as quickly as possible to tackle the current pandemic, but they will also need to maintain high rates of immunization against COVID-19 in the years ahead. Mass immunization campaigns need to be conducive to storage and distribution requirements for the vaccines themselves and avoid placing individuals at increased risk for infection. Public facilities with space for safe physical distancing measures (e.g. stadiums, cathedrals) and adequate power supplies in the case of cold chain storage may be used. Additionally, the workforce able to administer the vaccines will need to be boosted to support the tens of billions of vaccine dose administrations required. Healthcare systems can be creative and may look beyond doctors and nurses for this job. Furthermore, volunteers may be able to take on non-clinical tasks, such as directing patients, sanitizing waiting areas, and dolling out second appointment cards, to help vaccination rollout run smoothly.

A major concern in clinical systems is the administrative burden that the vaccines will have with their need for strong record keeping. Many of the first-generation vaccines require two doses spaced apart at set intervals which presents logistical challenges, especially in places without strong record keeping systems. Furthermore, we still do not know how long immunity from COVID-19 vaccines will last, and whether vaccine booster types can be mixed and matched. Emerging evidence suggests that just one dose of these two-dose vaccines may offer protection for those with previous COVID-19 infection [102,103]. Currently, however, the WHO has not listed any recommendations to test for COVID-19 antibodies before administering a vaccine. Thus, someone who may have already had the virus is still advised to get vaccinated when it is their 'turn' on the list. As the science develops and there becomes more clarity around how long immunity levels last after previous infection, this guidance could change. France's health authority, for example, issued recommendations in February that anyone previously infected with COVID-19 only receive one vaccine jab (even for vaccines in which two doses is standard); however, the agency did not issue any guidance on how it would determine who had already contracted COVID-19 and when [104].

Thus, providers of all specialties should be incentivized to monitor their patients' immunization histories and ensure vaccines are up-to-date, particularly if booster shots are required [95]. Phase 4 surveillance data could be made accessible to clinicians through publicly accessible platforms. Reporting systems can be finetuned and digitalized to ensure that clinicians are able to quickly and

**Table 2**
11 COVID-19 vaccine policy challenges.

| CHALLENGE | CURRENT ISSUES, POLICIES & PRACTICES | CONSIDERATIONS FOR THE FUTURE | FINANCING→ | ETHICS→ |
|---|---|---|---|---|
| *Ensuring continued development of safe and effective vaccines* | | | | |
| 1. Maintaining strong and sensible R&D incentives | • Direct grants, pre-purchasing agreements, and other financing mechanisms which do not attach strings to vaccine success outcomes | • Innovative financing mechanisms such as the Options Market for Vaccines (OMV) | | |
| 2. Running coordinated clinical trials | • Differences in organizing/reporting clinical trials between countries<br>• Issues related to diversity (age, race/ethnicity) of clinical trial participants<br>• WHO proposal for a Solidarity Vaccine Trial<br>• EU Clinical Trials register | • Uniform clinical trial criteria (including endpoints) could be developed<br>• Diverse sample of participants should be included in trials<br>Clinical trials for future vaccine candidates should be flexible | | |
| 3. Authorizing safe and effective vaccines efficiently and transparently: | • Regulatory timelines, guidance, and processes vary across countries<br>• Some agencies have authorized vaccines without stage III trial data<br>• Initial guidance around vaccines in older adults and pregnant women varied between regulatory bodies<br>• Regulatory guidance for vaccine modifications to address new variants differs across agencies | • Further alignment on regulatory processes is needed across jurisdictions<br>• Regulatory agencies should use same units and end points<br>• Transparency and efficiency<br>• Further alignment on fast-tracking COVID-19 vaccine updates to address new variants | | |
| 4. Monitoring effectiveness during (and after) vaccine deployment | • Domestic efforts to monitor vaccines that have been administered; but mainly independently run studies | • Consensus around the most useful post-market surveillance measures and how to report data in real-time to other nations<br>• International body, such as the WHO, could coordinate efforts of monitoring studies around the globe | | |
| Supplying and disseminating the vaccine around the world | | | | |
| 5. Ensuring equitable vaccine access globally | • Vaccine nationalism<br>• COVAX has made significant achievements, but much more funding is needed<br>• Countries are paying widely different prices for the same products<br>• Some HICs have committed to donating any extra vaccine doses to LMICs | • Global solidarity needed; COVID-19 is a threat to us all until everyone has access to a vaccines<br>• Greater investment in COVAX with guaranteed funding of $20-40 billion for 2021<br>• Innovative R&D financing models could link product price to the initial investments made and risk taken by a purchaser<br>• Plans should be established for COVID-19 donation processes<br>• Vaccine donations should be concurrent with national vaccination rollout | | |
| 6. Manufacturing sufficient quantities and maintaining supply chain capacity: | • Disruptions in the vaccine supply chain; delivery delays<br>• Some technology transfer agreements<br>• Cold chain requirements and ultra-cold chain requirements create logistical barriers – especially for LMICs<br>• Increasing concern around bottlenecks and shortages in supply chain equipment (e.g. vials, labels) | • Additional technology transfers between private companies<br>• Joint patent purchases for COVID-19 vaccines<br>• Compulsory licensing could be used to enable governments to gain control over production<br>• Increased cooperation between governments and private industry<br>• Removal of export bans on vaccines and supply chain equipment<br>• Gavi Board to bring co-investors on board to aid in building cold chain capacity in LMICs | | |

(*continued on next page*)

**Table 2** (*continued*)

| CHALLENGE | CURRENT ISSUES, POLICIES & PRACTICES | CONSIDERATIONS FOR THE FUTURE | FINANCING→ | ETHICS→ |
|---|---|---|---|---|
| Deploying the vaccine within countries | | | | |
| 7. Safely and securely transporting and delivering vaccines | • Global warnings about the potential for criminal activity aimed at infiltrating and disrupting COVID-19 vaccine supply chains<br>• Freight companies already enhancing security | • Continue security efforts and build new ones<br>• Security systems should protect the cargo and the integrity of the cargo | | |
| 8. Determining fair vaccine allocation: | • Most country allocation guidance prioritizes high-risk populations including elderly and co-morbid patients, critical health and social care workers | • Determine prioritization within high-risk groups<br>• Transparency around why some groups are placed higher on the list than others.<br>• Equity considerations should be made across and within priority groups<br>• Mechanisms should be established to capture groups that may otherwise be missed in prioritization schemes (e.g. undocumented migrants, homeless individuals) | | |
| 9. Encouraging the uptake of vaccines: | • Vaccine hesitancy, particularly amongst marginalized groups<br>• Anti-vax movement; fake news, misreporting, and an 'infodemic'<br>• Many individuals believe vaccine was developed too quickly | • Respond quickly, responsibly, and transparently if side-effects arise<br>• Flexible vaccine appointment times (24 hours)<br>• Inclusive vaccination campaigns; engage community leaders; sensitive to community contexts<br>• Science plus approaches; engagement/dialogue with vaccine hesitant people to understand/address concerns<br>• Celebrity vaccination campaigns<br>• Vaccine rollout strategies are not one-size-fits-all | | |
| 10. Ethical implications of vaccine passports and other vaccine requirements: | • Ethical debates and concerns around vaccine passports, employer/school vaccine requirements, etc.<br>• Some countries already launching vaccine passports<br>• Digital vaccine passports require considerations about data interoperability and more<br>• Ethical debates likely to increase if/when vaccines authorized in children | • Ethical dimensions must be considered, explored, and understood<br>• If vaccine passports or requirements are implemented, stipulations/exceptions need for those who cannot be immunized<br>• Legal considerations around vaccine passports (data interoperability, forgery risks, etc.) must be made | | |
| 11. Adapting Clinical and Health Research Systems | • Clinical system adaptations for vaccine campaigns underway in many countries<br>• Several authorized vaccines require two doses, spaced evenly apart<br>• The WHO does not currently recommend testing for antibodies for COVID-19 prior to administering a vaccine; France recommending previously infected individuals only receive one dose<br>• Some countries have established real-time surveillance and genomic sequencing systems; but efforts are not generally coordinated on the international level | • Public facilities with adequate opportunity for safe physical distancing measures and power supplies may be used for mass-administration clinics<br>• Healthcare systems can be creative and build training programs to increase personnel for vaccine administration<br>• Administrative capacity and incentive structures to facilitate record keeping needed<br>• COVID-19 vaccine and raw material stockpiles for future outbreaks due to antigenic drift or shift<br>• A global system based on the WHO's Global Influenza Surveillance and Response System (GISRS) | | |

securely report adverse health events associated with COVID-19 vaccines. Furthermore, health systems must maintain appropriately sized stockpiles of COVID-19 vaccines and raw materials for future outbreaks due to antigenic drift or shift.

Research systems also need to be adapted to efficiently detect virus mutations, share genetic sequencing globally, adjust existing vaccines, and develop new ones to respond to pathogens accordingly. Individual countries, such as the UK with its COG-UK, have had success in establishing real-time surveillance and genomic sequencing systems [105]. However, to be most successful, similar systems should be developed around the world and with coordination mechanisms between them. A global system based on the WHO's Global Influenza Surveillance and Response System (GISRS) whereby COVID-19 national research centers work under an agency within an international organization could be established so that COVID-19 epidemiology and genomic make-up can be monitored globally and alerts about novel variants can be made quickly [106].

## 5. Discussion

From start to finish, numerous policy challenges remain around COVID-19 vaccines, as outlined in Table 2. Estimates suggest that at least 60–70% of the population will need to be immune to COVID-19 to achieve herd immunity [107]. Furthermore, vaccines are vital components to the revitalization of economies and communities that have been devastated by the impacts of COVID-19 [108]. Thus, we must anticipate COVID-19 vaccine challenges and recognize their interdependencies in order to build actionable plans and ensure vaccine development, dissemination, and deployment. Equally, we must be realistic in our expectations of COVID-19 vaccines and their timelines given the multitude of barriers.

Global scientific partnerships have played an essential role in the successful delivery of COVID-19 vaccines so far. Thus, one of the key takeaways from the COVID-19 vaccine experience is that nationalistic approaches to immunization will not suffice, and global partnerships can be very successful and effective with the right resources. We have witnessed a truly great scientific feat, but this is not the end of COVID-19 and there are many other areas of unmet therapeutic need that we have not addressed yet. We must continue to support and fund these global efforts.

Luckily, a vaccine is not the only weapon against COVID-19 in our arsenal. Already, we have witnessed how successfully implementing non-pharmaceutical interventions, such as social distancing and mask wearing, can mitigate the spread of infection (although they do prevent complete re-opening of economies) [109]. We have also developed a deeper understanding of COVID-19 since it first emerged at the end of 2019, and identified several therapeutics to reduce risk of mortality in patients with the illness [110,111]. The successful vaccines that are emerging in the fight against COVID-19 are extraordinary developments, however they are just one tool in our shed of mechanisms to combat COVID-19, rather than a replacement of NPI and therapeutic methods.

The journey from vaccine discovery to global herd immunity against COVID-19 presents significant policy challenges that require collaborative, global responses. Despite the great success in bringing multiple vaccine candidates to market in under a year, there are still many challenges ahead for achieving herd immunity even at a national level, and much more so for achieving this at the global level. Decision-makers must be aware of these challenges and begin strategizing solutions that can be implemented at scale. Only then will the global public health community end this pandemic, while emerging prepared for the next.

## Declarations of Competing Interest

None.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.healthpol.2021.03.013.

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