Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment

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Summary

The COVID-19 pandemic is unlikely to end until there is global rollout of vaccines that protect against severe disease, and preferably drive herd immunity. Regulators in numerous countries have authorised or approved COVID-19 vaccines for human use, with more expected to be licensed in 2021. But having licensed vaccines is not enough to achieve global control of COVID-19: they also need to be produced at scale, priced affordably, allocated globally so that they are available where needed, and widely deployed in local communities. In this article, we review potential challenges to achieving each of the pillars and discuss implications for policy. To guide our review, we developed a dashboard to highlight key characteristics of 26 leading vaccine candidates, including efficacy levels, dosing regimens, storage requirements, prices, production capacities in 2021, and stocks reserved for low- and middle-income countries. We use a traffic-light system to signal the potential contributions of each candidate to achieving global vaccine immunity, highlighting important trade-offs that policymakers need to consider when developing and implementing vaccination programmes. While specific datapoints and their corresponding traffic-light categorisations are subject to change as the pandemic response progresses, the dashboard will continue to provide a useful lens through which to analyse the key issues affecting the use of COVID-19 vaccines. We also present original data from a 32-country survey (n=26,758) of potential acceptance of COVID-19 vaccines; the survey was conducted from October to December 2020. The share of respondents who said they would "definitely" or "probably" get vaccinated when a COVID-19 vaccine becomes available was highest in Vietnam (98%), followed by India and China (both 91%), and Denmark and South Korea (both 87%). The country that reported the lowest number of people who would "definitely" or "probably" get vaccinated was Serbia (38%), followed by Croatia (41%), France and Lebanon (both 44%), and Paraguay (51%).

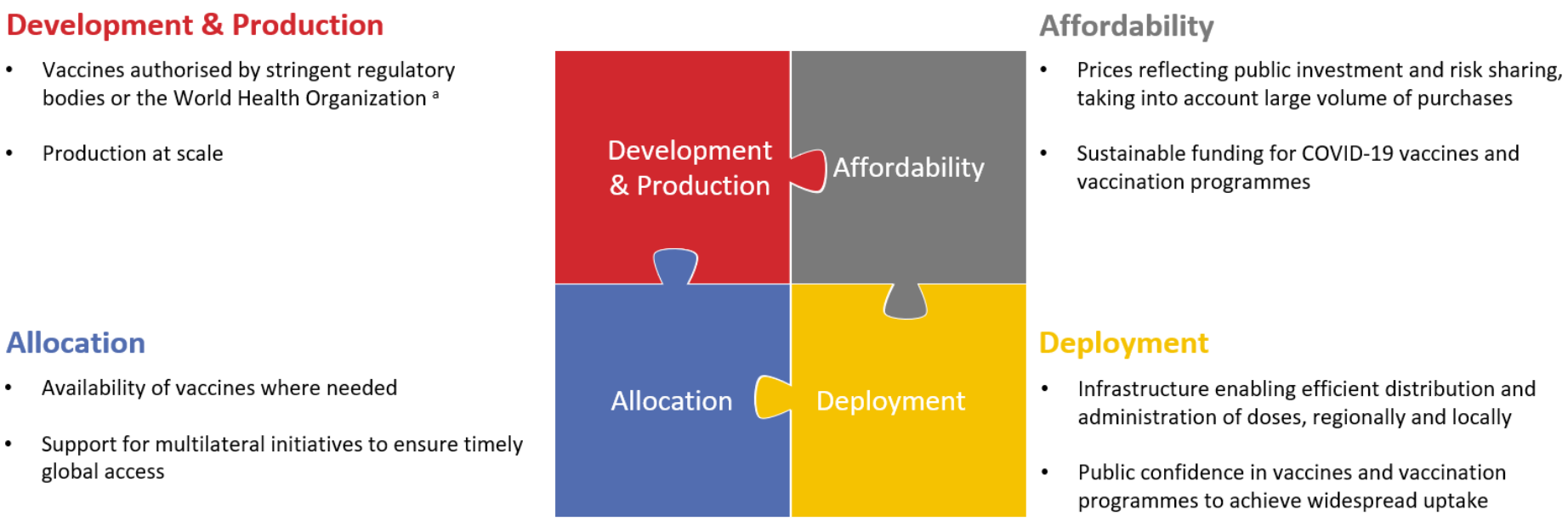
1. Introduction

The COVID-19 pandemic has caused substantial excess mortality[1] and plunged national economies into deep recessions.[2] Although the spread of the virus can be mitigated through physical distancing, face coverings, and testing and tracing—and potentially with therapeutics—the risk of outbreaks and disruption to economic and social life will likely remain until effective vaccines are administered to large portions of the global population to prevent hospitalisation and severe disease, and preferably achieve herd immunity to halt transmission of the virus.

Several COVID-19 vaccines have now been authorised or approved for human use, with many more in late stages of clinical development. Yet having licensed vaccines is not enough to achieve global control of COVID-19: they also need to be produced at scale, priced affordably, allocated globally so that they are available where needed, and widely deployed in local communities (**Figure 1**). The four pillars of the global vaccination challenge are closely related, and the development and production steps have important implications for pricing, allocation, and confidence.

In this article, we review potential challenges to achieving each of the pillars and discuss implications for policy. To guide our review, we developed a dashboard (**Table 1**) to highlight key characteristics of 26 leading vaccine candidates, based on the target product profiles for COVID-19 vaccines set by the World Health Organization (WHO). We focused on characteristics which distinguish individual vaccine candidates from one another. We use a traffic-light system to signal the potential contributions of each candidate to achieving global vaccine immunity, with red indicating there are high risks to achieving widespread immunity, amber indicating medium risk, and green meaning little or no risk. **Appendix 1** outlines the methodology for constructing the dashboard, including the criteria for assigning a green, amber, or red light for each characteristic. While specific datapoints and their corresponding traffic-light categorisations are subject to change as the pandemic response progresses, the dashboard will continue to provide a useful lens through which to analyse the key issues affecting the use of COVID-19 vaccines.

Figure 1. Four pillars of an effective global immunisation strategy against COVID-19.



[a] Stringent regulatory bodies may approve vaccines or authorise their use in emergencies (e.g. emergency use authorisation during public health crises, such as pandemics); the World Health Organization may grant vaccines emergency use listing (comparable to emergency use authorisation by a stringent body) or pre-qualification (comparable to approval by a stringent body). The World Health Organization publishes a list of stringent regulatory authorities.[3]

Table 1. Dashboard of key characteristics for leading vaccine candidates (grouped by pillar), with traffic-light system to signal the potential contributions of each candidate to achieving global vaccine immunity (as of February 3, 2021). [a]

	Development and production			Affordability	Allocation		Deployment	
Lead developers	**Authorised by stringent regulatory authority or the WHO** [b]	**Efficacy (interim ph. 3)** [c]	**Estimated production capacity (2021)**	**Lowest price offered (USD/course)** [d]	**% of doses pre-purchased by HICs based on known deals (2021)**	**Supply agreement with COVAX** [e]	**No. of doses**	**Storage requirement during transport**
AnGes / Osaka	-	-	-	-	-	No	2	-70°C
Anhui Zhifei / CAMS	-	-	300m	-	-	No	2 or 3	2°C to 8°C
AstraZeneca / Oxford	Yes	62% [f]	3bn	$5	27%	Yes	2	2°C to 8°C
Bharat Biotech	No	-	700m	$6	0%	No	2	2°C to 8°C
Biological E	-	-	-	-	-	No	2	2°C to 8°C
BioNTech / Pfizer	Yes	95%	2bn	$14	77%	Yes	2	-70°C
CAMS / IMB	-	-	-	-	-	No	2	2°C to 8°C
CanSino	-	-	320m *	-	0%	No	1	2°C to 8°C
Clover / Dynavax	-	-	1bn	-	-	No	2	2°C to 8°C
Covaxx	-	-	1bn	-	0%	No	2	2°C to 8°C
CureVac	-	-	300m	$24	100%	No	2	5°C
Gamaleya	Yes	92%	1bn	$6	0% [g]	No	2	-18°C
Inovio	-	-	100m	-	-	No	2	2°C to 8°C
Johnson & Johnson	-	66% [h]	1bn *	$9	38%	Yes	1 [i]	2°C to 8°C
Medicago	-	-	80m	-	100%	No	2	2°C to 8°C
Moderna	Yes	94%	1bn	$31	97%	No	2	-20°C
Novavax	-	89% [h,j]	2bn	$6	31%	Yes	2	2°C to 8°C
RIBSP	No	-	60m	-	-	No	2	2°C to 8°C
Sanofi / GSK	-	-	-	$19	73%	Yes	2	2°C to 8°C
SII / Max Planck Inst.	-	-	-	-	-	No	-	-50°C to -15°C
Sinopharm / Beijing Inst.	Yes	79% [h]	1bn	$62	8%	No	2	2°C to 8°C
Sinopharm / Wuhan Inst.	No	-	600m	$62	8%	No	2	2°C to 8°C
Sinovac	No	50% to 91% [h,k]	1bn	$21	18%	No	2	Room temp
SK Biosciences	-	-	-	-	-	No	-	2°C to 8°C
University of Hong Kong	-	-	-	-	-	No	-	-50°C to -15°C
Vector Inst.	No	-	11m	-	-	No	2	2°C to 8°C

Legend	Green: Yes Amber: --- Red: No	Green: ≥70% Amber: 50-69% Red: <50%	Green: ≥2bn Amber: 1bn-1.9bn Red: <1bn * For the assignment of risk levels, we treat a single dose of a 1-dose vaccine as equivalent to two doses of a 2-dose vaccine.	Green: <$10 Amber: $10-$19 Red: ≥$20	Green: ≤33% Amber: 34-66% Red: ≥67%	Green: Yes Amber: --- Red: No	Green: 1 Amber: 2 Red: ≥3	Green: Room temp Amber: Cold Red: Ultra cold

CAMS= Chinese Academy of Medical Sciences. GSK=GlaxoSmithKline. HIC=high-income country. IMB=Institute of Medical Biology (China). Inst.=Institute. ph.=phase. RIBSP=Research Institute for Biological Safety Problems (Kazakhstan). SII=Serum Institute of India. USD=United States dollars. WHO=World Health Organization.

[a] The sources and methodology are documented in Appendix 1. These candidates shown in this table have been approved or authorised on an emergency basis for human use in one or more countries, are in phase 3 clinical testing, or are under contract with the Coalition for Epidemic Preparedness Innovations or the COVAX Facility (as of February 3, 2021). Dashes indicate that either the data are unavailable, or it is too early to know (for vaccines in the earlier stages of development). Institut Pasteur (and its development partner Merck) and the University of Queensland were developing COVID-19 vaccine candidates with funding from the Coalition for Epidemic Preparedness Innovations, but these clinical trials have been discontinued.

[b] Only for vaccines which have been approved or granted emergency authorisation by at least one regulatory body. The WHO publishes a list of stringent regulatory authorities.[3] The WHO may grant vaccines emergency use listing or pre-qualification.

[c] Clinical trial designs, including efficacy endpoints, differed for the various vaccine candidates. Some of these efficacy figures may therefore not be perfectly comparable. Due to the emergence of new variants of the virus, the conditions under which trials take place vary; not all vaccines are tested against the same variants.

[d] These are the lowest price the developers offered to any country or purchasing bloc. Median prices for a range of countries are presented in Figure 2.

[e] Formally, the COVAX Facility also has a "first right of refusal for a potential combined total of over 1 billion doses in 2021" of vaccine candidates being developed by the companies funded by the Coalition for Epidemic Preparedness Innovations: Biological E, Clover, CureVac, Inovio, Moderna, Novavax, Oxford/AstraZeneca, SK Biosciences, and University of Hong Kong.[4]

[f] This was the result in the main efficacy analysis for participants receiving two standard doses, as specified in the protocol. The result in the out-of-protocol arm (half dose followed by standard dose) was 90%.

[g] One high-income country (Hungary) has purchased 2m doses, corresponding to 0.4% of all purchased doses. Due to rounding, the figure presented in the dashboard is 0%.

[h] These interim phase 3 results have not been published in peer-reviewed journals. The figures were sourced from press releases by companies or researchers running the clinical trials.

[i] The developer is also testing a two-dose version.

[j] This was the efficacy reported from a phase 3 trials in the United Kingdom. Novavax reported a lower efficacy level in a smaller phase 2b clinical trial in South Africa (49%). These results have not yet been published in peer-reviewed journals.

[k] Sinovac and its research partners have reported a range of efficacy levels based on phase 3 trials conducted in Brazil (50%), Indonesia (65%), Turkey (91%), and the United Arab Emirates (86%). None of these results have been published in peer-reviewed journals.

2. Development and production of COVID-19 vaccines

Several manufacturers successfully developed COVID-19 vaccines in under 12 months—an extraordinary achievement, given it typically takes a decade or longer to develop new vaccines.[5–8] The world now needs more doses of COVID-19 vaccines than any other vaccine in history in order to inoculate enough people to achieve global vaccine immunity.

Vaccines often suffer from under-investment,[9] but that has not been the case in this pandemic. As of February 3, 2021, there were 289 experimental COVID-19 vaccines in development, 66 of which were in different phases of clinical testing, including 20 in phase 3.[10] Only five of these 66 vaccines—those developed by AstraZeneca/Oxford, BioNTech/Pfizer, Gamaleya, Moderna, and Sinopharm/Beijing Institute—have been authorised by stringent regulatory authorities (as per WHO criteria of such authorities[3]) or the WHO (**Table 1**). Another five—from China, India, Kazakhstan, and Russia—have received approval or been authorised for emergency use by other regulatory agencies; some of these firms have submitted documentation to WHO for emergency use listing or pre-qualification, but these submissions are still under review.[11] Additional vaccines from Novavax and Johnson & Johnson are expected to be authorised based on positive interim phase 3 results. Several vaccines have demonstrated high levels of efficacy in clinical trials (>70%), although not all developers have published their results.

While public support for basic research and early-stage drug development is common,[12] the urgent need to develop COVID-19 vaccines and scale up supply has inspired new ways of aiding research, development, and production activities and enlist broad participation among private companies.[13] Governments and non-profit actors have financed clinical trials, invested in the building and expansion of production facilities, and established contract manufacturing and distribution networks to enable rapid rollout of successful vaccines.[14]

Table 2 summarises publicly available data on investments by governments and non-profit actors into the research, development, and production of advanced COVID-19 vaccine candidates. For more information see **Appendix 2**. The top five firms have each received between $957 million and $2.1 billion in funding commitments, mostly from the US government and the Coalition for Epidemic Preparedness Innovations (CEPI). The Chinese and Russian governments have invested in several vaccine candidates being developed by private firms or state-owned enterprises. Because many funding arrangements are confidential, details regarding the specific breakdown of spending are unclear.

Attention has now turned to expanding production capacity to promote widespread rollout of successful vaccines, as well as efficiently distributing them to centres for administration. Companies with leading candidates have reported widely different

supply capabilities through the end of 2021 (**Table 1**). Nine developers have said they will be able to produce at most 700 million doses each this year, while 10 other manufacturers have set production targets of 1 billion doses each or more. No single company will be able to supply all countries in this period.

Scaling up production to meet global demand is a monumental challenge.[15,16] Prior to this pandemic, there were no existing networks of contract manufacturers for several of the leading vaccine candidates that feature novel technologies, including those relying on messenger ribonucleic acid (mRNA) delivery platforms. And the volume of vaccines that are needed places pressures on global supply chains for inputs, like glass vials, syringes, and stabilising agents.

The production of COVID-19 vaccines is limited by the highly concentrated state of global vaccine manufacturing capacity,[17] and the relationships established between lead developers and contract manufacturers. A successful solution to the production bottleneck would likely require widespread technology transfer to enable the expansion of manufacturing capacity. Currently, few countries have domestic capacity to rapidly produce COVID-19 vaccines on their own, and instead would need firms to actively share knowledge, technology, and data with domestic manufacturers.[18] Some of the lead developers of COVID-19 vaccines have collaboration agreements with manufacturers in middle-income countries—for example, AstraZeneca with the Serum Institute (India), Fiocruz (Brazil), mAbxience Buenos Aires (Argentina), and Siam Bioscience (Thailand); Johnson & Johnson with Aspen (South Africa); and Novavax with the Serum Institute (India)—although the terms of these partnerships, including the extent to which the licensed manufacturers can negotiate their own supply arrangements with countries, are unclear.

Table 2. Public and non-profit funding for the research, development, and production of leading vaccine candidates (as of February 3, 2021). [a]

Lead developers	Technology	Known public and non-profit funding, US$	Funders
Sanofi / GSK	Protein subunit	$2.1 billion	US Govt
Novavax	Protein subunit	$2.1 billion	CEPI / Gates Foundation / US Govt
AstraZeneca / Oxford	Non-replicating viral vector	$1.7 billion	CEPI / UK Govt / US Govt
Johnson & Johnson	Non-replicating viral vector	$1.5 billion	US Govt
Moderna	mRNA	$957 million	CEPI / Dolly Parton COVID-19 Research Fund / US Govt
BioNTech / Pfizer	mRNA	$445 million	German Govt
Clover / Dynavax	Protein subunit	$430 million	CEPI / Gates Foundation
CureVac	mRNA	$348 million	CEPI / German Govt
Sinopharm / Wuhan Inst.	Inactivated	$142 million	Chinese Govt
Medicago	Virus-like particle	$137 million	Canadian Govt
Inovio	DNA	$107 million	CEPI / Gates Foundation / US Govt
Covaxx	Protein subunit	$15 million	Taiwanese Govt
SK Biosciences	Protein subunit	$14 million	CEPI / Gates Foundation
Biological E	Protein subunit	$9 million	CEPI / Gates Foundation / Indian Govt
University of Hong Kong	Replicating viral vector	$4 million	CEPI / Hong Kong Govt
CAMS / IMB	Inactivated	$3 million	Chinese Govt / Jack Ma Foundation
AnGes / Osaka	DNA	Unknown	Japanese Govt
Anhui Zhifei / CAMS	Protein subunit	Unknown	Chinese Govt
Bharat Biotech	Inactivated	Unknown	Indian Govt
CanSino	Non-replicating viral vector	Unknown	Unknown
Gamaleya	Non-replicating viral vector	Unknown	Russian Govt
RIBSP	Inactivated	Unknown	Kazakh Govt
SII / Max Planck Inst.	Live attenuated	Unknown	Unknown
Sinopharm / Beijing Inst.	Inactivated	Unknown	Chinese Govt
Sinovac	Inactivated	Unknown	Chinese Govt
Vector Inst.	Protein subunit	Unknown	Russian Govt

CAMS=Chinese Academy of Medical Sciences. CEPI=Coalition for Epidemic Preparedness Innovation. DNA=deoxyribonucleic acid. Govt=government. GSK=GlaxoSmithKline. IMB=Institute of Molecular Biology. Inst.=Institute. mRNA=messenger ribonucleic acid. SII=Serum Institute of India. UK=United Kingdom. US=United States.

[a] The sources and methodology are outlined in Appendix 2, which also includes more information about the funding arrangements. In brief, for companies with COVID-19 vaccines which have been approved or authorised for human use in one or more countries, are in phase 3 clinical testing, or are under contract with the Coalition for Epidemic Preparedness Innovations or the COVAX Facility, we searched press releases from companies and funders, as well as financial reports filed by companies with regulators in various countries, for information on public and non-profit funding. We did not count funds provided to licensees that produce and distribute vaccines on behalf of lead developers or to contract development and manufacturing organisations, nor did we count loans (i.e., debt financing) from international financial institutions (e.g., European Investment Bank). We included pre-purchase agreements between governments and companies where it appeared as though a significant portion of the funding went towards late-stage development (i.e., phase 1-3 trials) or scaling up production at risk prior to the completion of clinical testing.

3. Affordability of COVID-19 vaccines

Mechanisms are needed to ensure the affordability and sustainable financing of COVID-19 vaccines in low- and middle-income countries, which are home to about 85% of the global population and may lack resources to buy adequate quantities of vaccines.[19,20] Even in high-income countries, it is important to ensure access to COVID-19 vaccines for poor and marginalised populations.

Pricing

Firms have gradually been disclosing the prices they are offering to countries of different income levels, with marked variation in the lowest price per course (**Table 1**). Some firms, like AstraZeneca and Johnson & Johnson, which are benefiting heavily from public-sector investments, have pledged to sell their vaccines globally at low prices. Both firms have committed to maintaining these prices "during the pandemic",[21,22] although more clarity is needed to understand how it will be determined that the pandemic is over, as well as post-pandemic pricing models. These factors have implications for the durability of vaccination campaigns, especially if annual boosters will be required. Other companies are charging considerably more, with some firms setting prices that are among the highest of any in existence for vaccines (**Figure 2**). Some manufacturers are also planning to sell COVID-19 vaccines at a premium in private markets in countries like Bangladesh, Brazil, and India.[23–25] There are concerns that wealthier patients in these countries may gain quicker access to vaccines through these markets.

Multiple factors may drive the observed variation in prices. These include, for example, differences in technological platforms and the associated development and manufacturing costs; the amount of public funding that developers received; companies' diverse approaches toward licensing and the establishment of production networks; the extent to which COVID-19 vaccines fit into pharmaceutical firms' overall profit-making strategies; the presence of intellectual property rights; funders' demands (e.g., CEPI's access conditions); as well as political pressures on companies to keep prices low.

To illustrate how the prices of COVID-19 vaccines compare to those of other vaccines, **Figure 2** shows the median price per dose of existing vaccines by procurement or income group as of the end of 2018. Generally, countries covered by Gavi, a major buyer of vaccines for low-income countries, paid the lowest prices per dose (median across all vaccines, $0.57; interquartile range [IQR], $0.16-$1.9), followed by countries covered by UNICEF (median $0.80; IQR, $0.16-$2.8) and Pan American Health Organization (median $3.5, IQR, $0.87-$13.0), self-procuring middle-income countries (median, $5.3; IQR, $0.79-$18.3), and self-procuring high-income countries (median, $16.3; IQR, $6.5-$22.0).[26] Many self-procuring middle-income countries, which receive limited external

assistance, have historically been charged vaccine prices that are largely unrelated to income levels.[27]

Vaccine prices are especially important in the case of COVID-19, on account of the volumes demanded. Countries are aiming to administer COVID-19 vaccines to nearly their entire populations, potentially making these unaffordable for many governments, even at low per-dose prices. Depending on the duration of protection offered by these vaccines, as well as the potential need for modified vaccines that protect against new variants, these purchases could become recurring expenses.

Sustainable funding

To fund COVID-19 vaccines and vaccination programmes, including the costs of distribution, administration, record-keeping, and surveillance, governments will need substantial national revenue generation or external aid. Experiences with mass drug administration in previous health crises, for example HIV/AIDS, have shown that even when pharmaceutical products are inexpensive, or free, countries need financial support to both purchase and deploy them.[28,29]

These financial pressures are coming at a time when many economies are in crisis due the pandemic. If governments in resource-constrained settings divert resources from other vaccination programmes or essential health-care services to pay for COVID-19 vaccines and vaccination programmes, this could distort health budgets and have long-term adverse consequences for health and economic development.

Major donors and lenders, like the World Bank and other multilateral development banks, have earmarked billions of dollars in funds for COVID-19 vaccination programmes in low- and middle-income countries.[30,31] These funds can be used to buy vaccines which have been authorised by stringent regulatory bodies or the WHO. The G20's Debt Service Suspension Initiative may provide additional fiscal space too, by allowing the world's poorest countries to spread repayment of debt owed to other countries over extended periods of time. Though this initiative does not address debt owed to private creditors, the hope is that the temporary suspension of some repayments could release resources for more countries to better meet the costs of obtaining and administering vaccines.[32]

Figure 2. Median price per dose (US$) for all existing vaccines (2018) and for leading COVID-19 vaccine candidates (as of February 3, 2021) by procurement or country income group. [a]

GSK=GlaxoSmithKline. HIC=high-income country. J&J=Johnson & Johnson. MIC=middle-income country. PAHO=Pan American Health Organization. RF=Revolving Fund for Vaccine Procurement.

[a] Data obtained from the World Health Organization Global Vaccine Market Report.[26] Prices were not available for all procurement or income groups for all vaccines. Appendix 1 outlines the sources for all COVID-19 vaccine prices, which were obtained from press releases, investor documents, and media reports. The prices reported in this figure for COVID-19 vaccines are medians prices for each country group. These prices may therefore not match those reported in Table 2, which show the lowest price offered.
[b] Sinopharm is charging the same price for both of its vaccine candidates.

4. Global allocation of COVID-19 vaccines

In addition to needing vaccines to exist and to be affordable, a critically important pillar of the vaccination challenge is ensuring that enough doses are available globally. Current decisions regarding allocation are being made in the context of constrained supply, with demand exceeding current and projected levels of output.[17,33] Scarce supply, coupled with the large volumes of pre-orders made by high- and middle-income countries, creates challenges to achieving timely, universal access. Billions of individuals around the world may not have access to COVID-19 vaccines in 2021, which could prolong the pandemic and raise the risk of further mutations of the virus emerging, possibly undermining the efficacy of existing vaccines.

COVAX approach to global allocation

Uneven access to vaccines would not be unprecedented. During the 2009 H1N1 pandemic, rich countries bought up most of the global supply of pandemic influenza vaccines, leaving inadequate amounts for resource-poor countries, many of which were among the world's worst affected.[34,35] Some countries went as far as to block locally manufactured vaccine doses from being exported elsewhere,[36] something which EU member states are considering doing in the present pandemic too.

To avoid a repeat of the H1N1 scenario, in April 2020 the WHO announced the creation of a global allocation mechanism, the COVID-19 Vaccine Global Access (COVAX) Facility, coordinated jointly with CEPI and Gavi. COVAX is a pooled procurement initiative that, in addition to seeking to secure low prices, aims to provide all countries with access to a diversified portfolio of vaccines during the acute phase of the pandemic in 2021. Richer, self-financing countries can purchase vaccines from COVAX at an estimated average price of $11 per dose, while 92 poorer countries can receive them at considerably lower prices ($1.6 to $2 per dose), subsidised through official development assistance.[37]

At the core of the COVAX approach to global allocation is that vaccination should proceed in stages, with priority given to protecting older adults, health-care workers, and other high-risk individuals, before proceeding to vaccinate wider swaths of the population.[38] According to the COVAX model, all participating countries would initially receive enough stock for 20% of their populations, after which distribution would adhere to the WHO framework for allocating COVID-19 vaccines internationally based on need.[38] The over-arching logic of COVAX is that no country should vaccinate more than 20% of its population until all countries have vaccinated 20%, in accordance with principles of global equality. Others have suggested alternative allocation frameworks, though all share their roots in principles of fairness and ethics.[39–43]

Threats to equitable allocation

For COVAX to succeed, it needs substantial funding to purchase vaccines. As of February 2021, governments and other partners have committed around $4.0 billion in funding for COVAX,[44] but Gavi and the WHO estimate that a further $6.8 billon will be needed for COVAX to procure and deliver at least 2 billion doses by the end of 2021.[4,45]

A greater threat to equitable allocation comes from national procurement strategies that may leave COVAX with inadequate supply.[46–52] Many high-income countries have opted not to purchase their vaccines via COVAX, and instead have sought to gain priority access to abundant quantities of COVID-19 vaccines by striking advance purchase agreements with developers. The goal of such purchases is to secure access to enough vaccine to inoculate most, if not all, of countries' adult populations in 2021. Securing large quantities of vaccines in this way amounts to countries placing widespread inoculation of their own populations ahead of the vaccination of health-care workers and high-risk populations in poorer countries. Based on public records, governments in high-income countries—representing 16% of the global population[53]—have struck pre-orders covering at least 4.2 billion doses of COVID-19 vaccines. These countries have secured at least 70% of doses available in 2021 of five leading vaccine candidates, based on known deals (**Table 1**).

Though the pattern of purchasing vaccines directly from developers and not via COVAX began with high-income countries (including the EU as a unified buyer), numerous other countries have followed suit. This dynamic is self-reinforcing: as more countries procure doses directly, concerns about the reliability of COVAX's supply heighten, thus creating greater incentives for countries to procure doses on their own. The incentives to procure vaccines this way increases further after positive trial results are announced, which reduces the risk of advanced purchases for the successful vaccines. As of February 3, 2021, at least 62 countries or blocs of countries had signed purchase agreements with manufacturers.[54]

But not all countries can procure enough COVID-19 vaccines on their own. Instead, most countries are counting on COVAX, which has reached agreements with five companies (**Table 1**) for about 2 billion doses.[4] This amount could allow COVAX to achieve the goal of vaccinating 20% of the populations of participating countries. However, because it is unclear which vaccines will be distributed to which countries at what time, it is challenging for governments reliant on COVAX for doses to plan vaccination programmes. Similarly, uncertainty about COVAX supply complicates governments' decisions about how to acquire the best vaccine portfolios for their populations, including doses beyond those covered by COVAX.

Apart from the cross-country equity concerns raised by a scenario of 20% vaccination starting later in 2021 in poorer countries next to much wider (if not universal) vaccination starting and advancing earlier in richer countries, there is uncertainty about the supply earmarked for COVAX. Many of the doses secured by COVAX are of vaccines

that, as of February 2021, are just completing clinical trials and may not be available for months to come.[4] COVAX may also gain access to vaccines being developed by companies funded by CEPI that are not as far along in trials, and it may negotiate further agreements with other suppliers. Yet overall, COVAX's supply is precarious and depends on what happens to the vaccines in clinical trials, how much of the successful ones can be produced quickly, and how much of the output is left for COVAX after sales to national governments.

Though COVAX was originally created to achieve equality in the initial stages of vaccination, as all countries inoculate the first 20% of their populations, it is unlikely to achieve that goal. Instead, what COVAX can achieve, hopefully, is help countries procure doses at lower prices and thus launch their vaccination campaigns earlier than they would if left on their own. With additional funding, COVAX could likely compete better in the global scramble for vaccines and secure a place further toward the front of the queue.

Given scarce supply of some of the vaccines developed in Europe and the US (**Table 1**), governments in Latin America, Africa, the Middle East, and Asia have turned increasingly toward vaccines developed by Chinese, Indian, and Russian manufacturers.[55,56] These vaccines, which are far along in the development process, may relax the global supply constraint. To the extent that high-income countries continue to refrain from purchasing these products, their emergence may allow poorer countries to also procure abundant doses to achieve national vaccination goals. Though few have been authorised by the WHO or by regulatory authorities that the WHO classifies as stringent, as they do so, these vaccines could also contribute to the COVAX portfolio.

5. Deployment of COVID-19 vaccines

Beyond issues related to determining which countries will get vaccine doses when, and at what prices, it is essential to ensure the smooth deployment of COVID-19 vaccines. The rapid pace of production and development has shortened the time available for national, regional, and local health officials to plan training and preparedness for COVID-19 vaccination programmes.

Logistical and administrative challenges

Robust data infrastructure will be needed for local authorities to identify eligible individuals by priority group, send invitations, arrange transport for disabled and elderly patients, and (for some vaccines) recall individuals for their second doses. Several of the leading vaccine candidates require ultra-cold chains and have short shelf lives once they are removed from storage. BioNTech/Pfizer's vaccine, for instance, must be administered within 5 days of leaving ultra-low temperature conditions (-70°C);[57] similar, if less extreme, requirements apply to Moderna's mRNA vaccine. Strong coordination between workers at central depots and local vaccinators will be needed to ensure the timely and efficient distribution of batches to areas without freezers so doses of mRNA vaccines can be administered promptly.

Many low- and middle-income countries will face barriers in delivering vaccination programmes to adults, ensuring completion of two-dose vaccination schedules, and maintaining cold or ultra-cold supply chains. As of 2018, 74 of the 194 WHO member states had no adult vaccination programme for any disease, such as seasonal influenza; fewer than 11% of countries in Africa and South Asia reported having any such programme.[58] These countries may lack immunisation registries for adults and the storage, delivery, and waste management systems needed to administer vaccines at this scale.[58] It is worth noting that Gavi and its partners established ultra-cold supply chains in several sub-Saharan African countries after the 2013-2014 Ebola epidemic to deploy an Ebola vaccine developed by Merck which must be kept at -60°C to -80°C. However, this was done on a much smaller scale than what is currently needed, and would be prohibitively expensive for the global administration of vaccines in this pandemic.[59,60]

Several vaccines which only require refrigeration during transport have been authorised for human use, while a few single-dose products are in clinical development (**Table 1**). The availability of one-dose vaccines which can be kept refrigerated or at room temperature would greatly simplify the logistical and administrative challenges associated with COVID-19 vaccination programmes. Moreover, as scientific understanding of the properties of new vaccines (such as the thermal stability of mRNA vaccines) improves—or new ways of formulating these vaccines are developed—it is possible that logistical barriers may be lowered; this would make it easier to deploy such vaccines in resource-poor countries. Indeed, CureVac has an experimental mRNA

vaccine in late-stage clinical development which can be kept refrigerated. The product profiles of COVID-19 vaccines can help governments decide which vaccines to procure; these profiles, alongside any constraints reported by governments, can also help inform COVAX's allocation decisions. This may become increasingly important as additional, differentiated vaccines are authorised.

Beyond technical issues related to data and storage infrastructures, vaccination schedules, and other logistical matters, there are steps that governments can take to promote accountability, which may make COVID-19 vaccination campaigns more effective. These include, for example, transparency and clear communication on the part of government officials about timelines, the prioritisation of different groups for vaccination, the choice of vaccine products, and the design of administration schedules. This may require country-level monitoring and evaluation systems to track vaccine roll-out. This can help support the efficient running of campaigns, as well as continued population adherence to non-pharmaceutical interventions, like physical distancing and face coverings, as vaccination programmes are established and scaled up.

Vaccine hesitancy

Deployment can also be hampered by vaccine hesitancy,[61–71] which may lead to delayed acceptance or refusal of COVID-19 vaccines. Hesitancy is prevalent in poor and rich countries alike, with sceptics found in all socioeconomic, religious, and ethnic groups.

Figure 3 presents original data from a 32-country survey (n=26,758) of potential acceptance of COVID-19 vaccines conducted between October 21, 2020, and December 16, 2020. The share of respondents who said they would "definitely" or "probably" get vaccinated when a COVID-19 vaccine becomes available was highest in Vietnam (98%), followed by India and China (both 91%), and Denmark and South Korea (both 87%). The country that reported the lowest number of people who would "definitely" or "probably" get vaccinated was Serbia (38%), followed by Croatia (41%), France and Lebanon (both 44%), and Paraguay (51%).

Numerous other surveys of COVID-19 vaccine acceptance were conducted between March and October 2020.[72–76] While it is not possible to directly compare the results of all existing surveys of COVID-19 vaccine acceptance, due to differences in the countries included, questionnaires, and methodologies, these surveys overall seem to suggest that willingness to vaccinate against COVID-19 has declined globally between the early months of the pandemic and December, although rates tend to fluctuate.

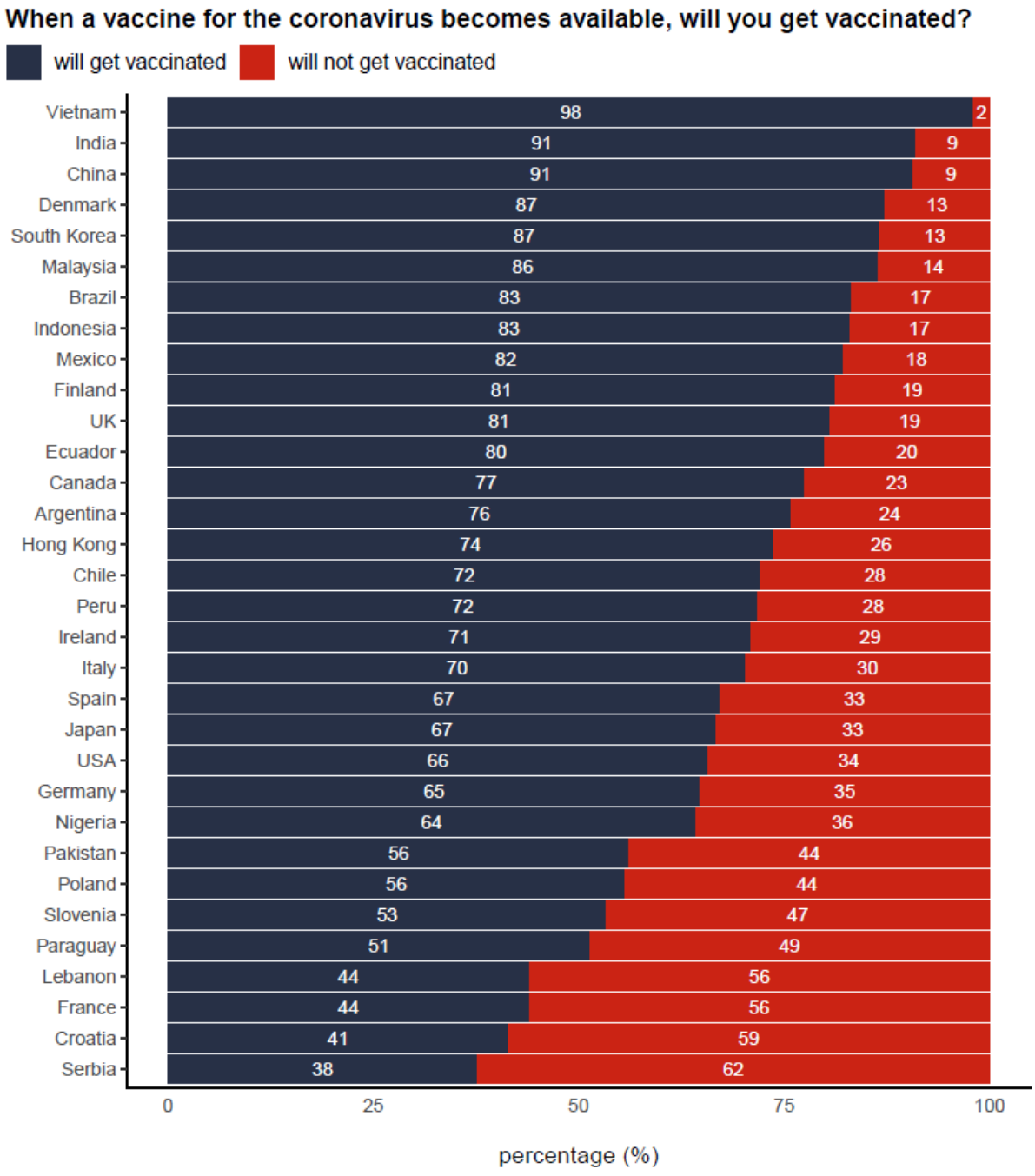
At least three issues are contributing to COVID-19 vaccine hesitancy. First, the speed at which vaccines have been developed, which reflects the unprecedented amount of funding from governments and non-profit groups, has raised concerns that they were rushed and regulatory standards relaxed,[77] concerns that were similarly reported

during the H1N1 pandemic.[78] Second, there are no previously approved mRNA vaccines, which also sparks hesitancy given the newness of these approaches. Third, conspiracy theories about COVID-19 vaccines are being widely circulated on unregulated social media platforms,[79–81] sometimes by highly organised anti-vaccination groups.[82–84]

The evidence to support measures to mitigate vaccine hesitancy and refusal is mixed, in part due to the wide range of strategies which have been used across settings for different vaccines and target groups.[85] Common elements across successful strategies include: (1) initiatives to increase vaccination knowledge and awareness; (2) community engagement, including involvement of religious and other influential leaders, to understand concerns, build trust, and manage rumours and misinformation; and (3) making vaccines available in convenient and accessible locations.[67,86–88] Having robust pharmacovigilance systems, alongside compensation schemes for severe adverse events, may help build confidence in vaccine safety in post-approval periods, especially in resource-poor countries with imperfect consumer protection systems.[89,90] Moreover, disadvantaged groups, many of which have suffered historical neglect and abuse,[91] often report lower levels of trust in the medical community[92,93] and lower uptake of health care interventions, including vaccines.[94–97] Additional efforts are needed to build trust among these groups.

Vaccine confidence may also be strengthened as more manufacturers obtain authorisation from stringent regulatory authorities or WHO, and as these bodies clearly communicate the rationale behind their decisions to the public. The approval of experimental COVID-19 vaccines by Chinese, Indian, and Russian regulators prior to the conduct of phase 3 trials has generated widespread consternation among regulators and scientists in some other countries because of the limited availability of safety and efficacy data and concerns that it could weaken confidence in vaccines.[56,98–102] The European Medicines Agency has also been subject to lobbying from several EU governments, who have urged the regulator to grant authorisation for the AstraZeneca/Oxford vaccine as soon as possible to expedite vaccination programmes.[103] Authorisations that are perceived to be premature may undermine trust in regulators, vaccines, and vaccination programmes.

Figure 3. Survey of potential acceptance of COVID-19 vaccines (October - December 2020). [a]



UK=United Kingdom. USA=United States of America.

[a] The data were jointly collected by the polling company ORB International and the Vaccine Confidence Project (London School of Hygiene & Tropical Medicine) between October 21, 2020, and December 16, 2020. Appendix 3 describes the survey methodology. The data were collected through telephone, online, and face-to-face interviewing, depending on the country; participants were recruited and verified locally. The agencies did not collect any personally identifiable data. Within each country, the sample ranged from 500 respondents (e.g., Lebanon) to 1,500 respondents (e.g., South Korea); 26,758 individuals participated in the survey. Samples were random and nationally representative of the adult population in 30 of the 32 countries. In Ecuador and Vietnam, interviews were only administered in the main cities

(Quito and Guayaquil, Ecuador; Hanoi and Ho Chi Minh City, Vietnam). Each respondent was asked, in the local language: “When a vaccine for the coronavirus becomes available, will you get vaccinated?” The possible responses were “definitely will”, “unsure but probably will”, “unsure but probably will not”, or “definitely will not”. In this figure, the category “will not get vaccinated” included respondents who said they “definitely will not” or “probably will not” get vaccinated. The category “will get vaccinated” included respondents who said they “definitely will” or “probably will” get vaccinated. Survey weights were applied to compensate for over- or under-sampling by sex, age, and sub-national region.

6. Discussion

Many commentators have called for a cooperative approach to vaccine allocation and deployment.[48,49] In doing so, appeals to norms of fairness and solidarity are common.[48] By contrast, the widespread disregard for a global approach to vaccine allocation demonstrated by national governments is a missed opportunity to maximise the common good by reducing the global death toll,[104] supporting widespread economic recovery,[105] and mitigating supply chain disruptions.[49] More equitable distribution of COVID-19 vaccines would help contain the pandemic sooner, and thus minimise the risk of new variants of the virus arising against which existing vaccines are less effective.

In this paper we have stressed the interactions among four pillars involved in the global COVID-19 vaccination challenge: development and production, affordability, allocation, and deployment. It is not enough to have new vaccines developed; they must be affordable, accessible, trusted, and, to maximise impact, utilised.

Governments and other vaccine purchasers must now decide which vaccines to procure, as well as how to secure funding for COVID-19 vaccines and vaccination programmes. To reach these decisions, government officials and partners in international organisations will need to assess the suitability of various vaccines for their respective health systems and populations—for example, in terms of availability, affordability, efficacy, and dosing and storage requirements.

The dashboard (**Table 1**) highlights trade-offs associated with leading COVID-19 vaccines with respect to these pillars. Multiple vaccines, for instance, are highly efficacious—exceeding the WHO's targets of 50% (minimum) and 70% (preferrable) efficacy—but require ultra-cold storage during transport or have little reserved capacity for low- and middle-income countries. And, while all currently authorised or approved vaccines require two doses, single-dose vaccines which can be stored at refrigerated temperatures are in late stages of clinical development; such vaccines would be easier to deploy in resource-constrained settings, which may lack infrastructure for delivering and administering two-dose vaccines reliably.

Differences in product characteristics may become particularly salient in 2021, while vaccines remain in short supply. If additional vaccines are successful in clinical testing and companies meet their production targets, then COVAX could allocate vaccines, in part, based on their suitability for local conditions. For instance, should single-dose vaccines which can be stored in refrigerators become available, then these could be prioritised for distribution in low- and middle-income countries that lack ultra-cold supply chains or national vaccine registries for two-dose regimens.

The dynamics of production and development have important implications for each of the other pillars. Governments and non-profit groups have committed unprecedented

sums towards the development of COVID-19 vaccines and the infrastructure to produce them at scale, which has helped companies develop new vaccines in record time. But affordability remains a concern, given the volume of doses that countries will need to purchase, and the additional expenditures that distributing and delivering vaccines entails. The extensive involvement of public funders in the development and production of COVID-19 vaccines provides them with opportunities to make these vaccines globally affordable. For vaccines developed by companies accepting external investment, funders that are sharing the financial risks could try to exercise leverage over the pricing of these products, as CEPI has aimed to do (with uncertain levels of success).[106,107] Funders could also negotiate clear timelines for the recovery of research, development, and production costs by companies; for example, initial doses might be sold at higher prices in the first year in rich countries and then closer to marginal cost in subsequent years.[108] Determining these price levels would require governments to audit the financial records of vaccine makers.

The allocation challenges discussed are also related to production: conflicts over priority access to scarce vaccine doses could be made less acute with greater output (i.e., were vaccine doses less scarce). To that end, the WHO has called for member states, manufacturers, and other organisations to commit to sharing knowledge, intellectual property, and data related to COVID-19 health technologies, through the COVID-19 Technology Access Pool (C-TAP). Similarly, several countries have proposed to suspend the World Trade Organization's (WTO) rules on intellectual property rights during the pandemic, suggesting that doing so could facilitate scaling-up. Yet as of February 2021, no manufacturers of leading vaccine candidates have engaged with C-TAP, and the WTO reform proposal has not gained traction.

Here too, the extensive public role in funding vaccine development potentially provides opportunities. Funders could encourage vaccine developers receiving public support to share their technologies and know-how systematically and widely, so to expand global production. And funders could work with developers to alleviate supply chain constraints and accelerate the scaling up of production. To the extent that international control of COVID-19 is regarded as a global priority, for example to slow the emergence of new, dangerous variants (against which some authorised vaccines may be less effective), governments may have an incentive to exercise these levers.

As important as developing and distributing safe, efficacious, and affordable vaccines around the world is the needed public confidence and trust in COVID-19 vaccines and those who deliver them to ensure uptake. Policy makers should urgently engage with communities to improve confidence in vaccines and combat misinformation and rumours around COVID-19. Post-marketing surveillance is important to build confidence during vaccine rollout. Developing successful, locally tailored strategies requires an understanding of contextual and historical influences of vaccine hesitancy and refusal.[78]

Equally, vaccine manufacturers should aim for maximum transparency and scrutiny of their clinical trial data to build public trust. It is in the interest of manufacturers and the public for preliminary data to be assessed by stringent regulatory bodies before these data are publicly released. Regulatory bodies safeguard public health by assessing whether the benefits of pharmaceuticals outweigh their risks. Regulatory decisions and their rationale should be clearly communicated to provide reassurance to the public that authorised products are safe and efficacious. Vaccine developers have a further reason for seeking approval or emergency use authorisation from a stringent regulatory body or WHO: only vaccines which have gone through one of these regulatory pathways will be eligible for purchase through COVAX or through funds made available by major development banks.

7. Conclusion

The societal value of safe and effective COVID-19 vaccines is enormous. Yet new vaccines will mean little to individuals around the world if they are unable to get vaccinated in a timely manner. This requires vaccines to be affordable and available to countries around the world, and for governments to have the administrative and political capacities to deliver them locally. In this paper we have discussed each of these four dimensions: production and development, affordability, allocation, and deployment; and the interactions between them. The distinct characteristics of leading COVID-19 vaccines across each of these dimensions generates trade-offs, which mean that both globally and nationally, the availability of diversified sets of vaccine options is likely to be needed to bring the global pandemic under control.

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