COVID-19 vaccines for low- and middle-income countries

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Received 4 November 2020; revised 18 February 2021; editorial decision 19 February 2021; accepted 24 February 2021

ABSTRACT

The COVID-19 pandemic is the biggest threat to public health in a century. Through hard work and ingenuity, scientists have developed a number of safe and effective vaccines against COVID-19 disease. However, demand far outstrips supply and countries around the world are competing for available vaccines. This review describes how low- and middle-income countries access COVID-19 vaccines, what is being done to distribute vaccines fairly as well as the challenges ahead.

KEYWORDS

2019 novel coronavirus disease clinical trial, covid-19, low- and middle- income countries, severe acute respiratory syndrome coronavirus 2, vaccines

Introduction

On 30 January 2020, the WHO declared coronavirus disease 2019 (COVID-19) as a Public Health Emergency of International Concern. Within 1 y, more than 103 million COVID-19 cases have been reported, resulting in over 2.2 million deaths worldwide. About 30% of cases and deaths were in Europe and another 30% in North America. Asia and South America account for approximately 22% and 15% of reported cases, respectively. Countries on the African continent have to date reported more than 3.5 million cases and over 90 000 deaths.[1] Among the 50 countries with the highest disease burden, 33 are developing or low- and middle-income countries (LMICs), accounting for more than half of the cases and deaths (Table 1). By 30 January 2021, Brazil and India had each reported around 10 million cases. Russia, Turkey, Colombia, Argentina, Mexico, Poland, South Africa, Iran, Ukraine, Peru and Indonesia all had over 1 million cases (Figure 1). Because most asymptomatic and mild infections are undocumented, published figures are likely to be underestimates of the true numbers. Due to a lack of testing and contact tracing, under-reporting and denial, some countries may have 10 times more cases than reported.[2,3] To date, Tanzania and North Korea have yet to confirm any cases and are officially coronavirus-free.

Even before the coronavirus pandemic, many people in the developing world were facing daily challenges such as crowded living quarters, poor sanitation, endemic malaria and HIV disease, as well as malnutrition. Overall, 80% of people with diabetes now live in LMICs, where it is more likely to be undiagnosed and poorly managed.[4] In places where essential services are chronically underfunded and have few intensive care facilities and limited hospital oxygen supply, a pandemic only exacerbates the existent inequalities in public access to healthcare. When COVID-19 arrived in the city of Manaus, the famed gateway to the Amazon in northern Brazil, over three-quarters of residents were infected.[5] Hospitals were overwhelmed, cemeteries ran out of space and doctors had to decide which COVID-19 patients to admit based on their chances of survival. In India, 56% of Delhi's 20 million residents were exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and were positive for COVID-19 antibodies, according to a national serology survey conducted in January 2021.[6] Many countries have introduced strict public health measures to reduce SARS-CoV-2 virus transmission. Policies like curfew, district lockdowns and requirements for personal protective equipment can dis-proportionally affect vulnerable populations that are socially and economically disadvantaged. For farmers and street vendors in LMICs who live from hand to mouth, social distancing and curfews can put their livelihoods in jeopardy and cause hardship.

LMICs are in urgent need of COVID-19 vaccines to avert a global catastrophe.

Vaccine development

The COVID-19 pandemic has caused immense difficulties and loss of life. In response, scientists have been racing against time to develop a growing portfolio of COVID-19 vaccines, from mRNA to inactivated whole virus to adenovirus-vector and protein

subunits. For a new vaccine to be approved by national regulators such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), scientists have to satisfy prespecified criteria in safety, clinical efficacy and product quality and manufacturing consistency. The FDA, EMA and the WHO have all agreed that new COVID-19 vaccines should have at least 50% efficacy in protection against COVID-19 disease in large- scale clinical trials.[7,8] Trial teams also have to accumulate at least 2 mo of participant safety data on vaccine side effects to evaluate the risks and benefits to be granted emergency use authorisation by the FDA. Once approved nationally, vaccine manufacturers can apply for WHO Emergency Use Listing (EUL) or prequalification, which should facilitate expedited regulatory approval in countries that do not have the capacity to perform comprehensive evaluation of medicinal products.[9,10] In addition to safety and effectiveness, the WHO also considers the stability and storage conditions of the new vaccines to see if they are suit- able for use in LMICs.[11] Vaccine candidates that require ultra- cold chain storage below 20°C are generally not eligible for WHO prequalification. But due to the exceptional circumstances of the COVID-19 pandemic, these candidates are also being considered.

Vaccine supply

Not every country has the technology and infrastructure to develop, test and manufacture new vaccines. Currently, there is a vacuum of vaccine manufacturing capacity in Africa and South America. As a result, many countries have to rely on others for vaccine supplies to save lives when a pandemic strikes. This opens the door to vaccine nationalism, where each country competes to leverage its purchasing power to secure vaccine doses for its own citizens, leaving behind vulnerable nations that are most in need. In the ideal world, anyone who needs a vaccine should be given one. But in reality, there are some hard questions that need answering. Who should get the vaccines first? To reduce mortality, you might want to protect the most vulnerable groups first. To reduce virus transmissions, one might want to first vaccinate young adults. To keep a nation running smoothly, governments might want to prioritise essential services and protect the workforce. Which countries should get the vaccines first? There are two schools of thoughts on the fair distribution of vaccines, namely equality and equity. Equality means each country should receive a number of vaccines proportional to the size of its population. Equity means vaccines should be allocated based on need. At the moment, there is a patchwork of different pathways for countries to access newly developed COVID-19 vaccines, including direct purchase, group financing and donations.

Direct Purchase

According to the Duke Global Health Innovation Center, individual countries have placed advance orders for a total of 7.1 billion doses of COVID-19 vaccines, 4.6 billion of which are going to developed countries. In other words, high-income countries have reserved 65% of all COVID-19 vaccines, despite only accounting for 16% of the world's total population (Figure 2).[12,13] This is partly a reflection that many wealthy countries, like the USA and the UK, made bilateral agreements with vaccine manufacturers early in 2020.

They invested billions of dollars in developing new vaccines and supporting their mass production in advance of approval. In return, these high-income countries receive the first batches of the vaccine doses as soon as they have been approved by regulatory authorities and are made available.

However, the situation is also the result of vaccine nationalism. Canada and the UK have locked up so much of the vaccine stock through advance marketing commitments that they should have enough to vaccinate their entire populations five and three times over, respectively. Such scrambling for COVID-19 vaccines is reminiscent of what happened during the 2009 H1N1 flu pandemic, when many LMICs in Africa were left behind. South Africa, the country most affected by COVID-19 in Africa, had to pay double the European Union (EU) price to access the AstraZeneca vaccines made by the Serum Institute of India (SII).[14] On the other hand, Israel reportedly paid 50% more than the market price to guarantee early access to the Pfizer/BioNTech vaccines. Israel finished vaccinating 80% of its senior citizens before many other countries had even started. To make the situation worse, EU vaccine manufacturers of the Pfizer/BioNTech and the AstraZeneca vaccines were unable to deliver orders on time, leading to vaccine shortages in Europe. This resulted in a public dis- agreement between AstraZeneca and the European Commission, which set up a mechanism to control vaccine export. In March 2021, Italy blocked a shipment of 250 000 doses of the AstraZeneca vaccines to Australia. This episode is a sobering reminder of the danger of over-reliance on any one region to make life-saving medicines and the urgent need to build domestic manufacturing capacity on every continent.

With American suppliers prioritising domestic demands and the EU facing vaccine shortages, countries around the world are increasingly turning to China and Russia. Unlike the West, both China and Russia are actively trying to increase their share of the global vaccine market.

Chinese vaccines

China has now granted authorisation for general use of four homegrown COVID-19 vaccines. The BBIBP-CorV inactivated vaccine manufactured by state-owned Sinopharm CNBG was reported to be 86% effective in a phase 3 trial conducted in the United Arab Emirates (UAE).[15] Sinopharm is supplying 130 million doses to developing countries such as Morocco, Egypt, Peru and Pakistan, as well as the EU states Hungary and Serbia.[12] Sinopharm will also partner with an Emirati company to produce at least million doses in the UAE.

The CoronaVac inactivated vaccine from Sinovac Biotech was found to be 50.4% effective against all symptomatic disease and 78% effective against mild to severe disease in its Brazilian phase 3 trial.[16] Sinovac had the capacity to produce 600 million doses of COVID-19 vaccine in 2020. Almost 390 million doses have been sold to developing countries, including Brazil, Chile and Turkey. Indonesia will receive enough bulk vaccine material to fill 40 million vials.

The third Chinese vaccine on the global market, Ad5-nCoV, is a single-shot virus-vector vaccine developed by CanSino Biologics and the People's Liberation Army. The company has sold over 70 million vaccine doses to LMICs, including Mexico and Pakistan, which hosted phase 3 efficacy trials of the vaccine and reported 65.7% protection against symptomatic diseases.[17]

Russian vaccine

The Sputnik V is a heterologous two-dose virus-vector vaccine developed by the Gamaleya Research Institute. During early development, it attracted criticism from the scientific community because Russia granted it state registration before the phase 3 efficacy trial had even begun. Nonetheless, the vaccine has been shown to be 91.6% effective and is now approved in at least 26 countries.[18] The Russian Direct Investment Fund has sold over 327 million doses of Sputnik V to 22 countries, mostly LMICs, including India, Vietnam, Uzbekistan, Mexico, Nepal, Egypt, Argentina, Venezuela and Brazil. When Argentina's contract negotiation with Pfizer collapsed in 2020, Russia stepped in. On Christmas Day, the first batch of 300 000 doses of Sputnik V was delivered to Buenos Aires on the 'Flight of Hope', winning hearts and minds as well as arms. In Hungary, regulators circumvented EU procedures to approve Sputnik V for emergency use and the country became the first EU member to administer the Russian vaccine.

COVAX facility

In order to provide fair access to COVID-19 vaccines for developing countries, the WHO partnered with the GAVI, the Vaccine Alliance and the Coalition for Epidemic Preparedness Innovations to create an innovative financing mechanism called the 'COVAX Facility'; 92 LMICs and economies are eligible to join.[19] Under this ambitious global initiative, over 145 participating countries, including China and EU member states, pool resources to purchase vaccines at affordable prices. The new US administration under President Biden has also agreed to join. By December 2020, the programme had raised US$2.4 billion and secured access to 2 billion doses of new COVID-19 vaccines. Different vaccines in the COVAX portfolio are being distributed according to a fair allocation mechanism, as they receive national approval and/or WHO EUL.[19]

During the initial phase, COVAX aims to provide vaccines to cover 3.3% of the total population of all participants, enough to protect the most vulnerable groups like healthcare workers.[20] Further doses will then be shared equally among participants to vaccinate up to 20% of populations to protect frontline workers, people aged ≥65 y and people with underlying medical conditions. Once that has been achieved, the programme will be expanded equitably to provide additional vaccines to countries with the highest risk.

In early March 2021, COVAX started rolling out an exceptional first batch of 1.2 million doses of the Pfizer/BioNTech mRNA vaccine after it was granted the WHO EUL.[10] This vaccine requires ultra-cold chain logistics. Sixteen LMICs plus South Korea and the Palestinian territories were selected for distribution according to their readiness and healthcare work exposure. These include Bhutan, Bolivia, Bosnia, Cabo Verde, Colombia, El Salvador, Georgia, Maldives, Moldova, Mongolia, Peru, Philippines, Rwanda, South Africa, Tunisia and Ukraine. Pfizer/BioNTech has agreed to provide a total of 40 million doses to COVAX at a not-for-profit price.

According to the COVAX Interim Distribution Forecast, the programme is also scheduled to deliver 336 million doses of the Oxford-AstraZeneca Ad26-vectored vaccine to 145 participating countries and territories. The SII will supply 240 million doses and the AstraZeneca-SKBio in South Korea will supply another 96 million doses. The vaccine was granted EUL by the WHO on 14 February 2021, in time for COVAX to ship 100 million

doses by the end of March and another 200 million by the end of July; 40% of the SII supply will be deployed within India and millions of doses will go to countries like Pakistan, Nigeria, Bangladesh, Ethiopia, Democratic Republic of the Congo, Myanmar, Kenya, Uganda and Sudan, Afghanistan, Uzbekistan, Angola, Ghana, Yemen, Cameroon and North Korea.[20] Of the South Korean stock, 2.6 million doses will be distributed within South Korea and millions have been allocated to Indonesia, Brazil, Mexico, Philippines, Egypt, Vietnam, Iran, South Africa, Columbia, Iraq, Argentina, Algeria, Canada and others.

Meanwhile, UNICEF, a COVAX delivery partner, has reached a 260 long-term vaccine supply agreement with SII to provide up to 1.1 billion doses of AstraZeneca vaccine and Novavax vaccine for LMICs. COVAX has also signed a Memorandum of Understanding with Johnson & Johnson to supply 500 million doses of its one dose COVID-19 vaccine. As most of the other COVID-19 vaccines require two doses, this gives the Johnson & Johnson vaccine an advantage, especially in LMICs, where population movements can dampen uptake of the second dose.

African Union

In general, a minimum of 60% to 70% vaccine coverage is required to create herd immunity. To top up the 20% coverage assured by COVAX, the African Vaccine Acquisition Task Team (AVATT) was set up to procure and deliver additional vaccines across Africa. Through AVATT, the African Union (AU) was able to secure 270 million doses of COVID-19 vaccines for the 55 AU member states.[21] The African Export-Import Bank (Afreximbank) is offering loans to individual AU member states to finance the immunisation program. Through this programme, countries can pre-order the Pfizer/BioNTech, Johnson & Johnson and AstraZeneca (branded “Covidshield” from SII) COVID-19 vaccines at a heavily discounted price. They would then pay back the loans in quarterly instalments over the next 5 to 7 years. According to the Africa Centres for Disease Control and Prevention, this is the first time Africa has secured millions of vaccine doses during a pandemic. The programme aims to provide at least 50 million vaccine doses from April to June 2021.

Vaccine Diplomacy

Because wealthy Western countries have reserved the majority of the initial COVID-19 vaccine doses produced in the USA and Europe, there is a huge unmet demand in developing countries and LMICs. This presents an opportunity for vaccine manufacturing powerhouses like India and China to fill this void before the COVAX mechanism swings into full operation.

China

In May 2020, China announced that Chinese-made COVID-19 vaccines will be a “global public good”, as the country’s contribution to ensure vaccine access for developing countries and that “African countries will be the first to benefit”.[22] To achieve this, China has built a cold-chain air bridge between Shenzhen in southern China and Addis Ababa, Ethiopia. The Chinese logistics firm, Cainiao, is partnering with Ethiopian Airlines to

distribute COVID-19 vaccines using temperature-controlled cargo planes and climate-controlled airport warehouse originally built for frozen food. Amidst the downturn in global aviation, the Shenzhen Bao'an International Airport was established as a "COVID-19 Vaccine Global Delivery Base", certified for pharmaceutical logistics and starting special vaccines flights to Africa and South America.[23]

Since February 2021, China has been donating the Sinopharm inactivated COVID-19 vaccine to LMICs, including 1.6 million doses for Pakistan and 1 million doses for Cambodia. China has promised to assist at least 53 developing countries with vaccines, including Belarus, Brunei, Mongolia, Palestine, Sierra Leone, and Zimbabwe. China has also pledged to donate 10 million vaccine doses to COVAX. In addition, China has offered a US$1 billion loan to South American and Caribbean countries to access Chinese COVID-19 vaccines.

India

India is home to the largest vaccine manufacturer in the world (SII) and stands in a good position to supply COVID-19 vaccines to LMICs across the globe. According to the External Affairs Ministry, India will donate 1 million doses of COVID-19 vaccines to COVAX and 10 million doses to African countries. The Indian government has even created the hashtag VaccineMaitri# (Vaccine Friendship) to raise the profile of this diplomatic initiative.

Under the Neighbourhood First foreign policy, India has been prioritising its South Asian neighbours and key partners. It has already donated over 5 million doses of COVID-19 vaccines to Afghanistan, Bangladesh, Bhutan, Maldives, Myanmar, Oman, Nepal and Sri Lanka. It has been reported that India will donate vaccines to at least 40 countries.

Vaccine hesitancy

Even in the middle of a pandemic, hesitancy towards newly approved COVID-19 vaccines is a big issue. Only 51% of adults in the USA said they would get a COVID-19 vaccine, with even lower acceptance among African Americans at 32%.[24] One third of US troops who have been offered a COVID-19 vaccine have declined it. Some vaccine sceptics worry that new vaccines have been approved in a rush, not knowing that most candidates have gone through vigorous assessment in multiple clinical trials. Some people are concerned about potential long-term side effects. Others object to the governments of China, India and Russia approving their vaccines without effectiveness data. There are people who reject all forms of infection control measures due to the perceived infringement on their civil liberties. As with other outbreaks, there are also people believing rumours and conspiracy theories, over the origin of the virus, the scale of the pandemic, the involvement of big pharmaceutical companies and infertility. To date, there is a paucity of COVID-19 vaccine trials in sub-Saharan Africa (SSA), with the notable exception of South Africa. But the very notion of testing COVID-19 vaccines in SSA has been met with fierce resistance in some African countries. In April 2020, two prominent French scientists appeared on live television proposing to test BCG vaccines to prevent COVID-19 in Africa, "where there are no masks, no treatments and no resuscitation". That

comment has been interpreted as treating “Africans as human guinea pigs”, provoking public outcry and seeding mistrust against COVID-19 vaccines in Africa. Each type of vaccine refusal will require a different mitigation strategy, but honesty and clear communications will always be key.

Vaccine effectiveness

The degree of vaccine protection observed in the idealised environment of clinical trials (efficacy) could be different to the level of protection seen in the real world (effectiveness). Although we have yet to see the full impact of mass vaccination campaigns on the COVID-19 pandemic, preliminary post-licensure data coming out of Israel have offered a glimpse of hope. Israel started mass vaccinations in December 2020 for people aged >60 y and people in at risk groups. In total, 3.5 million Israelis, over half of the eligible population, had received one or two doses of the Pfizer/BioNTech vaccine by February 2020.[25] In a study of nearly 1.2 million Israelis, half vaccinated and half unvaccinated, the two-dose mRNA vaccine showed 94% effectiveness against symptomatic disease; close to the 95% vaccine efficacy initially reported in the phase 3 trial in the USA. Despite the high prevalence of the UK variant of concern (VOC) during the study period (up to 80%), the vaccine significantly reduced the number of hospitalisation, severe cases and deaths from COVID-19.[26]

Efficacy gradient

Some vaccines can give a variable degree of protection in countries with a different disease burden, a phenomenon called efficacy gradient. Malaria coinfection is known to suppress vaccine immunity.[27] Rotavirus vaccines are more effective amongst children in developed countries with a low mortality rate than those in developing countries with a high mortality rate.[28] Even within a national immunisation programme, it is possible for economically disadvantaged people to have lower vaccine protection than others.[29] It would be important to see if COVID-19 vaccines are equally protective in developed countries and in LMICs where malaria and HIV are endemic.

People living with HIV

According to UNAIDS, 38 million people worldwide were living with HIV in 2019. The vast majority of them come from LMICs and globally only 67% are accessing antiretroviral therapy (ART).[30] HIV infection is associated with chronic inflammation and immune activation, which can accelerate the ageing process of the immune system, rendering it less responsive. As a result, HIV-positive individuals may have lower seroconversion rates and impaired antibody responses upon vaccination against influenza, tetanus, hepatitis A and B, as well as pneumococcus.[31,32] In order to study COVID-19 vaccination of HIV-positive 400 individuals, the Oxford-AstraZeneca phase 1/2 vaccine trials in the UK and South Africa include small HIV-positive cohorts to study vaccine responses and side effects. HIV-positive volunteers were recruited to see if they respond to the vaccine as well as HIV-negative volunteers, if this is affected by CD4 count and if vaccination has an impact on the HIV reservoir. The results should inform vaccine rollout in areas with high HIV prevalence. In the Novavax South African trial, the vaccine efficacy among HIV-negative participants was 60%, but the vaccine efficacy for HIV-positive and HIV-negative

participants was lower at 49%.[33] However, these figures have large confidence intervals and there were less than 300 HIV-positive participants, so the difference might not be statistically significant. People living with HIV may have more comorbidities, like diabetes, which predispose them to more severe COVID-19 disease. However, there is not enough evidence to conclude whether HIV-positive individuals diagnosed with COVID-19 are more likely to be hospitalised or have poorer outcomes. According to CDC, HIV-positive individuals who have a low CD4 cell count or are not on ART might have a higher risk of contracting severe COVID-19 disease.[34] People with an impaired immune system might not be able to mount sufficient innate defence and antibody responses to clear the SARS-CoV-2 virus during the first stage of infection.[35] Therefore, some immunocompromised people with COVID-19 might harbour the virus for longer and remain infectious for longer.[36] On the other hand, having a weakened immune system that is less likely to overreact during the second stage of infection might be protective against lung damage and complications driven by cytokines.[37] It has been hypothesised that chronic infection of immunocompromised people allows the virus to accumulate multiple mutations over time. Upon receiving convalescent plasma treatment, viruses in the immunocompromised patients might undergo selection, giving rise to new variants with antibody resistance.[38]

Adenovirus 5 vectored vaccines

There are some concerns over the use of adenovirus 5 (Ad5)-based vaccines in populations with a high prevalence of HIV. Ad5 virus vector is used in the second dose of Sputnik V as well as the single-shot COVID-19 vaccine developed by CanSino Biologics. Back in 2007, there were two randomised controlled trials testing an Ad5-based vaccine against HIV. The 'Step' trial took place in the Americas, Australia and the Caribbean; and the 'Phambili' trial was carried out in South Africa. Both studies found a significant increase in HIV infections among vaccinated men, especially those with pre-existing antibodies against Ad5 and/or those who were uncircumcised.[39,40] Therefore, some scientists have cautioned against using Ad5-based COVID-19 vaccines in populations with a high prevalence of HIV, for fear of increasing HIV transmissions.[41]

New variants

Like other RNA viruses, SARS-CoV-2 has been evolving constantly. Since its discovery in Wuhan, China, the virus has been mutating at a rate of one or two genetic changes per month. In early February 2020, the so-called "D614G" variant emerged in Europe and quickly replaced the initial virus to become the dominant pandemic virus around the world. Three new virus variants isolated in the UK (B.1.1.7), South Africa (B.1.351) and Brazil (P.1) rapidly gained prevalence and spread across borders from late 2020 onwards.[42] They were designated "variants of concern" (VOC) because they might (1) transmit more easily between humans, (2) escape immune control by first-generation COVID-19 vaccines, (3) avoid detection by certain PCR assays or (4) be associated with a higher risk of hospitalisation and death.

The origins of these VOC viruses are unclear. They emerged independently and share some common mutations, such as N501Y and E484K in the receptor binding domain (RBD) of the spike protein that decorates the virus surface. Because SARS-CoV-2 uses

the RBD region to bind receptors to human cells to gain entry, mutations here could affect virus infectivity, making the virus more easily transmittable between humans. The UK VOC was found to be 50% more transmissible.[43] Currently, the majority of approved COVID-19 vaccines target the spike protein. The level of anti-spike antibodies can predict vaccine protection in monkey experiments and is the focus of vaccine development. Mutations in the spike protein can potentially diminish antibody recognition of the virus. For instance, the E484K mutation can help virus variants to escape neutralisation by serum antibodies from recovered COVID-19 patients.[44] This could mean that people who had been infected by the non-VOC virus are susceptible to reinfection by a VOC virus, potentially making it more difficult to achieve herd immunity.

Scientists are now working to see if the emergence of these VOC also affects the efficacy of existing COVID-19 vaccines. It is believed that the higher the efficacy and level of neutralising antibodies a vaccine has against the original virus, the more likely it is that it will work against new variants. The Pfizer/BioNTech, Moderna and Oxford teams have already started working on new vaccines that match the new VOC, much like what is being done annually in the seasonal flu vaccination programme.

Pfizer/BioNTech and Moderna vaccines

There are no clinical trial data on the specific efficacy of these mRNA vaccines against the VOC viruses. However, the national mass vaccination campaign in Israel has successfully used the Pfizer/BioNTech vaccine to reduce the number new COVID-19 cases, hospitalisations as well as deaths, despite the UK VOC becoming dominant in the country.[26] This is corroborated by laboratory analyses of blood samples from vaccinees that found little or no loss of antibody neutralising ability towards the UK variant.[45] Similarly, the levels of antibody neutralisation towards mutations found in the South African and Brazil VOC are reduced but are still above the threshold of protection.[46] Therefore, these mRNA vaccines should be able to protect people against the three new variants.

Oxford-AstraZeneca vaccine

In the Oxford-AstraZeneca vaccine trials in the UK and South Africa, scientists identified participants who were infected and sequenced their coronaviruses. Reanalyses of the trial data found that the vaccine is 74.6% protective against symptomatic COVID-19 disease caused by the UK variant from Kent. [47] However, the same vaccine only provided minimal protection against mild or moderate COVID-19 disease caused by the South Africa VOC (Table 2).[48] In laboratory experiments, serum antibodies from vaccinated participants were either less able or unable to neutralise the South African virus. As a result, South Africa has decided not to use the 1 million doses of AstraZeneca vaccines it has purchased from the SII. In February 2021, the Africa CDC recommended using the AstraZeneca vaccine in countries that do not have the South African VOC in circulation.

Novavax vaccine

Novavax has been conducting phase 3 vaccine efficacy trial in the UK and a phase 2b trial in South Africa. In the UK trial, 50% of the detected COVID-19 cases among British participants were caused by the UK VOC. The vaccine was 95.6% effective against the non-VOC virus and 85.6% effective against the UK VOC.[33] In the South African trial, 9

out of 10 cases among participants were caused by the South African VOC. Despite multiple immune escape mutations in the South African VOC, the protein subunit vaccine was 60% effective against symptomatic COVID-19 diseases caused by the variant virus.[33]

Johnson & Johnson vaccine

The Johnson & Johnson COVID-19 vaccine is a one-dose vaccine currently seeking WHO approval for EUL. In the US phase 3 trial, the vaccine was 72% effective in protecting against moderate and severe disease.[49] Virtually all of the sequenced cases in the US trial, belong to the D614G pandemic virus. In. Brazil, the vaccine was 68.1% effective and over two-thirds of the sequenced cases were caused by the P.2 variant, which is different from the P.1 Brazilian VOC. In South Africa where nearly all the cases were due to the South African VOC, the vaccine is 57% effective.[49] South Africa will use the Johnson & Johnson COVID-19 vaccine to kick off its national campaign to immunize 1.25 million healthcare workers.

STRETCHING VACCINE SUPPLY

In this time of vaccine shortage, various strategies have been proposed to cover the maximum number of people.

Single dose

If you split a course of two-dose vaccine into two courses of one-dose vaccine, you can double the number of people immunised. Data from multiple phase 3 trials have shown that many COVID-19 vaccines that are designed to be two-dose may actually offer significant protection after the first dose. For instance, one dose of the Pfizer/BioNTech vaccine showed 88.9% efficacy and one dose of the Moderna vaccine had 80.2% efficacy.[50,51] Similarly, further analysis of the Oxford-AstraZeneca phase 3 global trial revealed that the vaccine provided 76% of protection against symptomatic disease 3 wk after one dose.[52] This was confirmed in a study of 5.4 million people during the initial vaccine rollout in Scotland, where one dose of the Pfizer/BioNTech vaccine and one dose of the Oxford-AstraZeneca vaccine were 85% and 94% effective in preventing COVID-19 related hospitalisation, respectively.[53] A single dose of the Pfizer/BioNTech vaccine was also found to protect against asymptomatic infection amongst healthcare workers.[54] In fact, the Johnson &Johnson Ad26.COV2.S vaccine, as well as the CanSino Ad5-nCoV vaccine, were both designed to be single dose and each is effective at preventing symptomatic disease after one shot.[17,49] Nonetheless, non-live attenuated vaccines usually need multiple doses to give durable protection. In general, a second dose is needed to improve antibody quality, boost the level of neutralising antibodies, facilitate affinity maturation and increase the functions of cellular responses.

Delayed second dose

When there are not enough vaccine doses, you might want to give more people some degree of protection by delaying the second dose instead of giving a small number of people the full protection. This was the rationale behind the UK government’s decision to extend the interval between the two doses to 12 wk for all COVID-19 vaccines given in

the UK. It was controversial at the time, partly because of the concern that immunity might wane during the long gap between doses.[55] The Pfizer/BioNTech vaccine was originally designed to be given 3 wk apart and the Oxford-AstraZeneca vaccine had a target interval of 4 wk. In further analysis of the Oxford-AstraZeneca global phase 3 trials, extending the interval between dose 1 and dose 2 from < 6 wk to > 12 weeks was found to double the antibody level.[52] There was also a stepwise increase in vaccine protection from 54.9% to 82.4%. Nonetheless, it is not known if these improvements will also apply to other COVID-19 vaccines.

Mix and Match

Mixing different brands of vaccine against the same pathogen is not uncommon for routine immunisation. When the supplies of different COVID-19 vaccines are unstable and the distribution logistics are challenging, mixing and matching vaccines can offer some operational flexibility in times of uncertainty. Scientists are now conducting non-inferiority trials to see if vaccine mixing (e.g. one dose of the Pfizer/BioNTech vaccine followed by one dose of Oxford-AstraZeneca vaccine) would give the same immunity as the original two-dose regimens.

CONCLUSIONS

We are very fortunate in that at least nine safe and effective vaccines have been developed within the first year of the COVID-19 pandemic. As the WHO Director-General Dr Tedros Adhanom has said, “the fastest way to end this pandemic and to reopen economies is to start by protecting the highest risk populations everywhere, rather than the entire populations of just some countries. Sharing finite supply strategically and globally is in each country's national interest”.[56] Viruses know no boundaries. In this interconnected world, no one is safe until everyone is safe.

AUTHOR’S STATEMENTS

Author’s contribution: EMC has undertaken all the duties of authorship and is guarantor of the paper.

Funding: None.

Conflicts of interest: None declared.

Ethical approval: Not required.

Data availability: The sources of all scientific data presented in this article have been cited.

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Table 1. COVID-19 disease burden of the 50 most affected countries. These countries are categorised as developed, developing or low- and middle-income countries according to allocations published by the Organisation for Economic Co-operation and Development (OECD) and the International Congress of Qualitative Inquiry (ICQI). The data shown are extracted from World-o-meter as of 30 January 2021.

Top 50 countries affected by COVID-19	Reported cases	Reported deaths
Developed countries	47,578,966	946,339
Developing countries	8,010,550	168,162
Low & middle income countries	40,517,910	968,049
Total	96,107,426	2,082,550

Figure 1. Global distribution of COVID-19 cases reported by low- and middle-income countries. This figure charts the number of cases recorded by World-o-meter up to 30 January 2021, 1 y after the WHO had declared COVID-19 as a Public Health Emergency of International Concern.

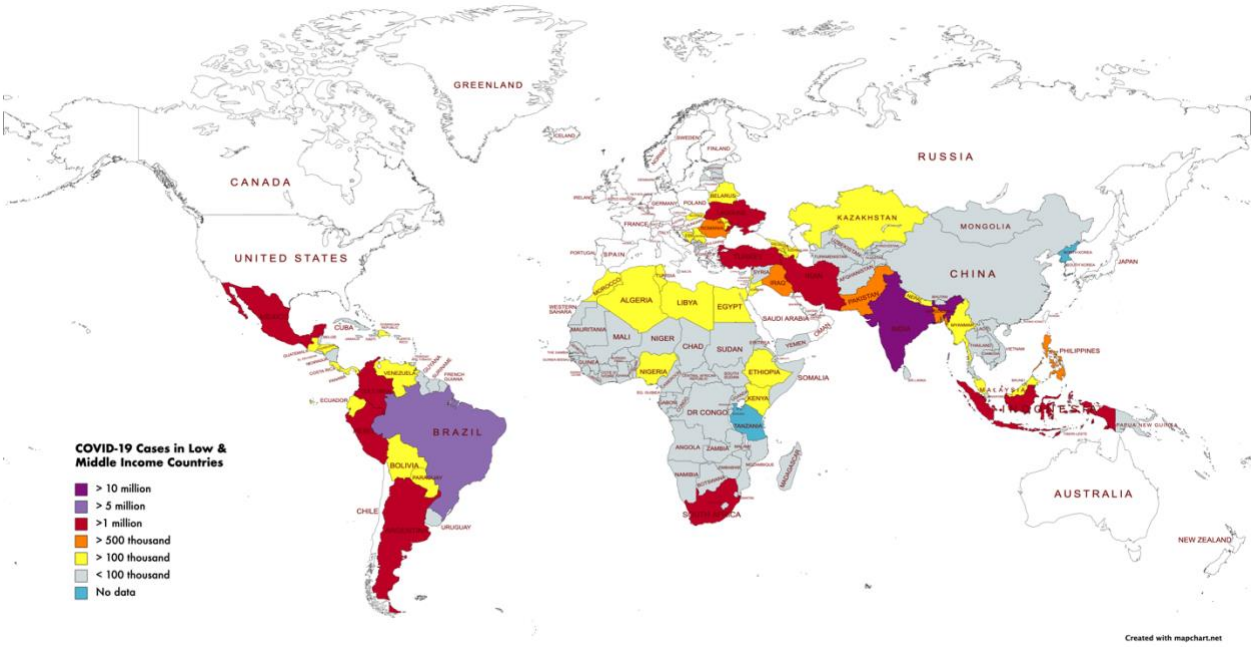

Figure 2. Global distribution of COVID-19 direct orders vs populations. Calculations were made using 2019 population figures released by the World Bank and the numbers of confirmed vaccine purchases published by The Duke Global Health Innovation Center.

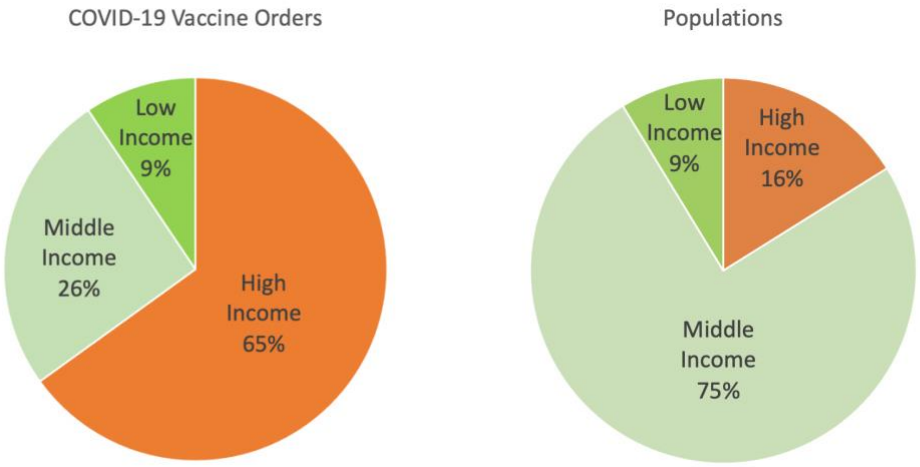

Table 2. COVID-19 vaccine efficacy against different variants of concern (VOC) in phase 2B/3 clinical trials

COVID-19 Vaccines	Non-VOC virus	UK VOC B.1.1.7	South African VOC B.1.351	Brazil VOC P.1
Pfizer/BioNTech	95%	(see text)		
Moderna	94.1%			
Oxford-AstraZeneca	84%	74.6%	10%	
Novavax	95.6%	85.6%	60%	
Johnson & Johnson	72%		57%	(see text)