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Covid-19 Vaccine Realism: The Good News and the Bad News

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Published at https://institute.global/policy/covid-19-vaccine-realism-good-news-and-bad-news on November 12 2020

Foreword by Peter Piot

As someone who has spent their career fighting viruses ranging from Ebola to HIV, I have witnessed first-hand the disruptive and tragic consequences that these dangerous pathogens can have. I believe that the Covid-19 pandemic is the greatest challenge in peacetime facing the world for more than 100 years, and the sobering reality is that we are only at the beginning.

This pandemic is not going away any time soon, and we must shift our thinking to see ourselves as societies living with this virus for the long-term. In our quest to adapt to a new normal we must continue to fight for the rights of health for all, not just for the privileged few.

Covid-19 is a pandemic of inequality. Hotspots around the world are emerging along the fault lines in our societies. And it is clear that this virus respects no borders. As long as one country in the world remains impacted by Covid-19, no country is safe. Solidarity is crucial to defeating this virus.

Vaccines are an incredibly powerful tool in public health. Equitable access to rigorously tested, safe and effective vaccines against Covid-19 is a fundamental priority for governments around the world. But we also know that vaccines alone are insufficient to stop the pandemic. They are not a silver bullet. Testing and effective contact tracing systems, good hand hygiene practices, social distancing, diagnostics, therapeutics, face coverings and personal protective equipment will all remain necessary until this virus can be brought to heel.

Concerted international efforts are required to overcome the major vaccination hurdles which range from discovery, to clinical development, multiple phases of clinical trials, licensure, to manufacturing on a huge scale as well as the major challenge of implementing immunisation programmes against the backdrop of increased vaccine hesitancy in many locations.

To curb this pandemic, it will not be enough for the richest countries to have a vaccine. Low- and middle-income countries need it too. Protecting the most vulnerable is not only the right thing to do but history tells us that this can be done as has been shown with access to antiretroviral therapy for HIV, achieved in low-income settings through perseverance and innovative solutions.

Covid-19 is first and foremost about people, not numbers or statistics. Communities and people must be at the forefront of our efforts and be active partners in any future response. Given the scale of the pandemic, it is essential that the public are part of the conversation and are brought along in the story around vaccines. This paper aims to do just that by clearly setting out the key developments – the good news and the bad – along with the major priorities and challenges that lie ahead.

Professor Peter Piot
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Introduction

The global race to find a vaccine to stop Covid-19 has progressed significantly, characterised by clinical development unfolding at a rapid pace, with processes that normally take 15 to 20 years condensed into mere months. Several vaccine candidates are currently in phase III clinical trials, which means that one or even more vaccines could be registered with regulators within the coming weeks and months. On 9 November, the Pfizer/BioNTech collaboration moved closer to approval with the announcement that their Covid-19 vaccine candidate showed a 90 per cent efficacy rate after seven days, tested in 43,500 people enrolled in phase III clinical trials; no safety issues were detected. [1] The data have not been peer-reviewed and it is unclear at this point what the durability of the protection is. More data need to be collected. The UK government announced on 10 November that it was ready to start rolling out the Pfizer/BioNTech vaccine and raised the possibility that it could be ready to begin by Christmas. Pfizer is seeking an emergency use authorisation this month.

Depending on efficacy rates, any approved vaccine could be a game-changer for the populations on which it is expected to be most effective. [2] For those who may become infected, a Covid-19 vaccine could lessen the severity of symptoms (this is how the influenza vaccine operates), which in more extreme cases have led to hospitalisation and death, and for survivors often mean long-term, debilitating health problems. Estimates are that vaccine(s) that make it to market may achieve a floor of 50 per cent efficacy, which is roughly the same as an influenza vaccine. To date the novel coronavirus (SARS-CoV-2) has exhibited less mutation as compared to influenza; [3] this means that it is more likely to be responsive to a vaccine-induced response. [4] It is unclear how long the protection conferred by vaccination will last; boosters may be required. Overall, this is encouraging news. But it is only part of the story.

Since the publication of our earlier paper, *Towards a Global Vaccine Strategy*, a number of issues have emerged that merit attention. The UK – along with numerous countries – is facing a surge in new infections, increases in hospitalisations, continued stress on the economy and pandemic fatigue, all of which are unsustainable. The new lockdown in the UK will take an additional toll on an already weakened economy. Moreover, the data about the long-term effects of Covid-19 on people who recover – even on people who are asymptomatic – are alarming. Long Covid will be costly for both people and health systems. These realities make the deployment of a vaccine critical.

Several key messages emerge from an analysis of the current landscape.

- First, there are measures that could be taken to decrease the amount of time it will take for a vaccine to be made available to the public, without sacrificing safety, jeopardising efficacy or undermining clinical development. Regulators have at their disposal a "rolling review," which accelerates the assessment of a promising vaccine or medicine when there is a public-health emergency; the

regulator reviews data from studies as they come in, before the decision is made to submit a formal application. [5] Subsequent rolling reviews from large-scale trials can assess vaccine efficacy and quality. This approach can eliminate weeks and possibly months from the process, increasing the likelihood that life-saving vaccines come to market more expeditiously. The UK's Medicines and Healthcare products Regulatory Agency (MHRA) only recently began a rolling review of AstraZeneca's (AZ) vaccine candidate, while the EU's and Canada's regulators initiated them (for AZ's vaccine candidate and Moderna's vaccine candidate, respectively) in October. Rolling reviews are critical and should be the standard for reviewing all Covid-19 vaccine candidates.

- Second, the perfect should not be the enemy of the good. Once safety is established, we should highlight the immense value of administering vaccines that may have lower efficacy levels than initially sought. Given the difficulty in arresting the virus and the alarming effects of Long Covid, a vaccine with a floor of 50 per cent efficacy would still be a game-changer in terms of allowing people to return to work and restarting the economy on a consistent basis, without repeated lockdowns.
- Third, the current lockdown provides the UK government with the opportunity to prepare for rollout of a vaccination programme. The UK has the most diversified vaccine candidate portfolio (340 million doses with options for more) and includes entrants from: AZ, Pfizer/BioNTech, Johnson & Johnson (J&J), Novavax, Sanofi/GlaxoSmithKline (GSK), and Valneva (see Table 4, included in the Annex to this paper). Public information indicates that AZ, Pfizer, J&J and Novavax are likely to have mature phase III clinical data available in December, indicating that they could soon be ready for rollout. Except for the Pfizer vaccine, the others use common vaccine development techniques. Pfizer uses an mRNA platform that has never successfully been scaled for a human vaccine.
- Fourth, vaccination rollout plans will depend, in part, on which vaccines are deployed. AZ's and J&J's vaccine candidates can be stored between 2° and 8°C and can be administered at a doctor's office or pharmacy, while Pfizer's requires storage at -70°C and will require special procedures and precision operations to deliver (see Annex Table 2). J&J is testing a single-dose shot while the others are two-shot vaccines that must be administered within 28 days of each other. These considerations will inform how the programme is structured and executed.
- Fifth, data on the UK's vulnerable population, frontline workers, current hotspots and so on should guide and revise the government's prioritisation of who should be vaccinated first. The reality is that there will not be enough doses to immediately vaccinate the entire UK population, so prioritisation will be necessary. Circumstances may change by the end of England's latest lockdown. A robust data tracking and management system will be necessary to guide decision-making and the actual vaccination process.
- Finally, the UK government should consider partnering with the Vaccine Confidence Project at the London School of Hygiene & Tropical Medicine on a public information campaign to prepare the British people for the vaccination campaign. Vaccine uptake requires public trust in government. The current trust deficit must be addressed immediately and needs to be an ongoing effort.

This second, national lockdown must be productive, not just in terms of slowing the virus but in the development of a vaccination plan that is accompanied by a robust, clear public-information plan that prepares the British people for what is to come.

This paper covers the following:

- The status of clinical development, with a focus on those that have entered phase III trials
- A review of the leading vaccine candidates with respect to issues such as how they are administered (nasal or injection), ease of administration and anticipated degree of immunity
- Deals made between drug makers and governments, highlighting access and equity for low- and middle-income countries
- The geopolitics of Covid-19 vaccines

Vaccine Efficacy and Strategy

The frenzy and desperation surrounding a Covid-19 vaccine has generated optimism that does not align with reality. Expectations for what a Covid-19 vaccine can accomplish need to be tempered; the hard reality is that vaccines are not a silver bullet for addressing the pandemic. Rather, they are an important part of a larger toolkit to manage and contain it, along with rapid, mass testing and contract tracing; social distancing; good hand hygiene; masks; and therapeutics. There are some instances where vaccines achieve a high rate of protection and near-to-complete elimination of transmissibility (such as the polio vaccine), but this may not be the case with the first generation of Covid-19 vaccine candidates that are closest to registration. The design of the phase III protocols of the leading candidate vaccines (made by AstraZeneca, Johnson & Johnson, Pfizer, and Moderna) are such that we may not have a clear answer as to whether they stop severe forms of Covid-19, and whether they halt the virus's transmissibility.

The effectiveness of any vaccine will also depend on how much of the population actually receives it. To drive the pandemic to the point of eradication will require a significant portion of the population to either acquire immunity through being infected with the virus (it is unclear how long Covid-19 antibodies remain in the immune system, but evidence suggests that they decline fairly quickly – in a matter of months), or through vaccination. [6] The UK government just announced its Covid-19 immunisation strategy, which will target only the most vulnerable. The UK's population is roughly 67 million people; about 30 million will receive the vaccination. The advice released on 25 September by the government's Department of Health and Social Care prioritised the following populations [7]:

- Older adults' resident in a care home and care home workers
- All those 80 years of age and over and health- and social-care workers
- All those 75 years of age and over
- All those 70 years of age and over
- All those 65 years of age and over
- High-risk adults under 65 years of age
- Moderate-risk adults under 65 years of age
- All those 60 years of age and over
- All those 55 years of age and over
- All those 50 years of age and over
- And the rest of the population (priority to be determined)

In summary, the UK is taking a shielding approach, prioritising those who are most at risk. However, the data indicate that infections are happening quickly among younger people. It may be prudent to vaccinate both older, high-risk groups as well as the demographic responsible for the most infections at the same time. Data and heat maps will be central to determining the best course of action.

While governments around the world are likely to deploy a range of vaccination strategies, they are in a similar position with respect to challenges in dealing with the public. Given the expectation that a vaccine will be available soon, political leaders, public-health experts and the drug companies themselves would serve the public well by launching a mass public-information campaign guided by vaccine realism so as to increase the likelihood of the public support needed for widespread uptake for groups targeted for vaccination. Populations in groups prioritised for vaccination will be more or less receptive based on the carrier of the message, how it is carried and what is communicated. [8] Vaccine hesitancy could undermine immunisation campaigns, so public trust must be built – a point supported by research by the Vaccine Confidence Project. [9] At the same time, pharmaceutical companies should respond positively to the calls for greater transparency about the nature of the phase III clinical trials, their protocols, their endpoints, the questions they are asking, and so on. Drug companies assume the risk for the very expensive costs associated with drug development; it is also the case that they have been supported by billions of dollars in taxpayer money in a range of countries, which makes public accountability appropriate, even as their intellectual property must be protected.

The Status of Clinical Development

As of 29 September 2020, there are 248 Covid-19 vaccine candidates under development. [10] Table 1, included in the Annex, shows the ones that have entered clinical trials. The breakdown is as follows:

- Pre-clinical (pre-human work): 199
- Phase I (small N safety trial): 22
- Phase II (larger N safety trial): 2
- Phase III (assessing efficacy with large N): 10
- Approved (market ready): 0

Only 11 out of the more than 200 under development have reached phase III clinical trials, the final stage before regulatory approval, registration, up-scaling of production and public access. All the candidates that have reached phase III are administered via intramuscular injection. [11] This trial phase evaluates safety and efficacy in a large sample (in the tens of thousands) across multiple sites, and with high-risk individuals, with a view towards identifying rarer side effects that may not surface during earlier phases. China leads with four candidates: Sinopharm has two while CanSino and Sinovac Biotech have one each; the US has three in the race, with one by Johnson & Johnson/Janssen and two under development by Pfizer in collaboration with Moderna and BioNTech, respectively. The UK has two possibilities, led by AstraZeneca and GSK. Russia's Gamaleya Research Institute's candidate is already being deployed outside the newly launched trial. Finally, Australia has one entrant in the final phase: a repurposed tuberculosis vaccine being trialled by the University of Melbourne.

J&J/Janssen has begun phase III clinical trials that will enrol up to 60,000 participants, including older people (who tend to respond less favourably to vaccinations) and those with underlying conditions that increase their likelihood of contracting Covid-19. [12] Moreover, the trial includes participants from Brazil, Mexico, South Africa and the United States; there will be "significant representation from Alaskan Native, American Indian, Black and Hispanic individuals, as well as those over age 60. The trial will include adults with and without co-morbidities associated with an increased risk for severe COVID-19." [13] This diversity is critical for ensuring that the vaccine is effective in particularly vulnerable populations. Moderna, the Massachusetts-based biotech firm, entered phase III trials in July with its mRNA candidate and will test 30,000 participants. The University of Melbourne in collaboration with Murdoch Children's Research Institute is taking a slightly different tack, with its phase III trial of a 100-year-old tuberculosis vaccine, Bacillus Calmette-Guerin (BCG). American giant Pfizer, and its German biotech partner BioNTech, are carrying out a combined phase II/III trial of BNT162b2, an mRNA vaccine, with more than 40,000 participants.

CoronaVac, developed by China's Sinovac, was trialling its inactivated virus in 9,000 health-care workers in Brazil, along with additional volunteers from Indonesia and Bangladesh. The Brazilian regulator announced on 10 November that it was suspending the trial after a Brazilian participant died after a "serious, adverse incident". The company claims that the death was not related to the vaccine. [14] Sinopharm's as yet unnamed vaccine candidate is being trialled with 15,000 people in the UAE, with additional phase III trials planned for Bahrain and Peru. However, hospital workers and other high-risk groups have already received the vaccine. [15] Meanwhile in China, Sinopharm and Sinovac have seen their vaccine candidates administered to more than 350,000 under an emergency use authorisation (EUA) that was granted in June. Expansion beyond prioritised groups is occurring, as Sinopharm is working with broadcaster Phoenix TV and Huawei to vaccinate their employees. [16] The Beijing city government is receiving tens of thousands of Sinovac's CoronaVac, while CanSino's viral vector vaccine, Ad5-nCoV, received approval from the Chinese government amid its phase II trial to vaccinate its military for one year; the phase III trial was announced by Petrovax, a Russian biopharmaceutical company.

While China's expansive use of homegrown vaccine candidates has generated alarm among some in the scientific community, its government's actions must be seen in the context of a country on which the virus has taken a heavy toll; the pressure to prevent a resurgence is enormous. There are, however, issues with respect to determining efficacy by administering vaccine candidates on a large scale outside the parameters of a rigorous phase III trial, given the fact that China has been successful in containing community spread; moreover, travellers arriving are quarantined. [17] Assessing efficacy in such a context is difficult. Russia's Sputnik V, developed by The Gamaleya National Center of Epidemiology and Microbiology, has been registered and is already in widespread use despite not having completed phase III clinical trials. Latin America (Mexico and Brazil), Russia and several Gulf countries (Saudi Arabia and UAE) will host phase III trials with 2,000 volunteers.

Vaccine Administration and Anticipated Immunity

J&J began its phase III trials later than the other companies but may have a few advantages (as compared with other candidates that use a sub-protein unit approach). First, its Covid-19 vaccine candidate is made using a proven platform – adenovirus – which has delivered effective vaccines for Ebola, Zika and other illnesses. Second, it is a single dose vaccine while many others require two doses administered roughly four weeks apart. Finally, storage temperatures for the J&J vaccine candidate do not require additional infrastructure. [18] While the vaccine must be shipped frozen, it can be stored at refrigerator temperatures for up to three months.

Issues such as the vaccine platform and associated storage temperatures matter greatly for ease of administration. For example, Pfizer/BioNTech's vaccine candidate, BNT162b2, must be stored at -94°F. [19] Pfizer has developed a process to safely ship the vaccine. The doses will be stored on dry ice, packed inside specially created thermal containers. Packages will have GPS-traced thermal sensors to monitor temperature and location to mitigate theft and accidents. Upon arrival at vaccination points (community centres, hospitals, pharmacies, etc.), the vaccine can be stored on new dry ice for up to 15 days, inside a refrigeration unit for up to 5 days, or in specialised ultra-low temperature freezers for up to six months. [20] Moderna's storage requirement of -4°F is an improvement over the Pfizer/BioNTech candidate. Moderna (whose vaccine candidate uses an mRNA platform) is working to demonstrate that its vaccine candidate can be shipped and stored at higher temperatures [21]; mRNA vaccine candidates that require sub-zero storage temperatures are more challenging to distribute to traditional points of delivery such as pharmacies, community health centres or doctor's offices. In the absence of innovative storage solutions, such vaccines would require specialised facilities such as laboratories and tertiary hospitals that could administer them in high-volume, one-day vaccination events; only a small number of people could be covered in such settings, however (see Annex Table 2). [22] Pfizer has developed a solution to address this challenge and Moderna is working on one, as well. For mRNA vaccine candidates that have not developed solutions, such requirements could put their makers at a competitive disadvantage, given the scale of the rollout necessary to achieve coverage. mRNA vaccine candidates do have an advantage in that they can be manufactured at scale quickly and easily because of the technology platform, and they induce strong immune responses. [23] Vaccine candidates based on protein sub-units do not have such stringent storage requirements, which makes them more appealing for massive, global immunisation efforts. All these features matter for logistics, distribution and actual administration, particularly in poor countries that lack the kind of physical and institutional infrastructure to administer mRNA vaccines. Finally, traditional approaches used by companies such as J&J and AstraZeneca have yielded vaccine candidates that are more affordable, with the former's costing USD $10 with a price

ceiling of USD $20, and AstraZeneca's carrying a price tag of USD $4 per injection. This matters greatly for low- and middle-income countries that simply do not have the budgets available for expensive vaccines. Bill Gates has proposed a three-tier pricing structure with poor countries paying the marginal costs, middle-income countries paying some of the fixed costs and rich countries paying much of the fixed costs to make a vaccine. [24]

That several vaccine candidates have entered phase III clinical trials obscures some of the complex realities that lie behind seemingly encouraging progress. The public's common understanding of vaccines is that they *prevent* illness. Take the measles, mumps and rubella (MMR) vaccine, for example. According to the US Centres for Disease Control and Prevention (CDC):

"[The] MMR vaccine is very effective at protecting people against measles, mumps, and rubella, and preventing the complications caused by these diseases. People who received two doses of MMR vaccine as children according to the U.S. vaccination schedule are **usually considered protected for life** and don't need a booster dose. An additional dose may be needed if you are at risk because of a mumps outbreak.

"One dose of MMR vaccine is 93 per cent effective against measles, 78 per cent effective against mumps, and 97 per cent effective against rubella. Two doses of MMR vaccine are 97 per cent effective against measles and 88 per cent effective against mumps." [25]

The CDC also points out that in the relatively few cases where someone who has received the MMR vaccine does become sick, their symptoms are mild. In these instances, it could be the case that their immune system's infection-fighting ability declined over time, or that their immune systems were insufficiently responsive to the vaccine. [26] The material point is that public expectation is that vaccines prevent serious illness and that they prevent transmission of pathogens that cause disease.

What requires clarification for the public is what the phase III clinical trials are actually addressing (see Annex Table 3.) A Covid-19 vaccine candidate that reaches approval may not necessarily end the pandemic, since the information about current trials indicates that efforts are focused mainly on addressing Covid-19 symptoms (which can range from mild to moderate to severe), and not on arresting transmission of the virus that causes Covid-19: SARS-CoV-2. The authoritative and respected *The Lancet* points out that "… the impact of these COVID-19 vaccines on infection and thus transmission is not being assessed. Even if vaccines were able to confer protection from disease, they might not reduce transmission similarly." [27]

The phase III clinical trials of the leading Covid-19 vaccine candidates that are in development by AstraZeneca, Pfizer, and Moderna are not designed to address the question of whether they prevent moderate and severe forms of the disease, which goes directly to the issue of worthwhile efficacy. [28] The companies released the protocols for phase III, all of which indicate that " . . . a vaccine could meet the companies' benchmark for **success if it lowered the risk of mild Covid-19, but was never shown to**

reduce moderate or severe forms of the disease, or the risk of hospitalization, admissions to the intensive care unit or death." [29] [Emphasis added.] By this criterion, trials could be stopped before such a determination is made. In all three trials – if they are allowed to operate for enough time – efficacy determination will happen when between 150 and 160 people develop Covid-19. [30] To determine their vaccine candidates' efficacy and potentially whether the trials can end early, the companies will evaluate the data various times over the course of the trials: AstraZeneca once; Moderna two times; and Pfizer, four times. [31] The accumulation of more evidence beyond 150 to 160 participants would be more likely to allow for the surfacing of both mild (most common cases) and moderate to severe cases of Covid-19, along with other potential problems (such as fatal reactions), which is critical given the expectation that potentially billions of people will eventually be vaccinated. This point is related to the make-up of the trial with respect to its diversity. Healthy people are less likely to develop moderate to severe cases of Covid-19, while those with underlying conditions or who are elderly are more at-risk. This is why testing of vaccine candidates to prevent infection with SARS-CoV-2 in older people is important; higher rates of sickness and death from Covid-19 are associated with older age.

The vaccine development process does not end when approval happens. There is a critical role that phase IV post-marketing surveillance studies can play in establishing long-term safety profiles of the new vaccine products. Hence common health surveillance and data systems across nations – real world studies that take place after and to complement the vaccine RCTs, would gather data about the multiple vaccine products in use and effects on various demographics and ethnicities. Oracle, as part of its Health Sciences Global Business Unit, has already established its Health Management System, which has a module specifically designed to capture such data in a privacy-protecting manner. Vaccinated citizens can use their mobile devices to easily report mild, moderate or severe adverse vaccine reactions and overall well-being. Medical providers and governments are able to aggregate this data by flexible cohorts and determine adverse patterns by manufacturer, lot, geography, demographic and so on.

Pfizer announced that it submitted an amended protocol. "The proposed expansion would allow the companies to further increase trial population diversity, and include adolescents as young as 16 years of age and people with chronic, stable HIV (human immunodeficiency viruses), Hepatitis C, or Hepatitis B infection, as well as provide additional safety and efficacy data." [32] The trial will evaluate the vaccine candidate's effectiveness in the amended, larger study. While Pfizer's recent announcement about efficacy was encouraging, questions still remain about the vaccine's performance with respect to the sub-groups referenced above. Moreover, it is unclear how well the elderly will respond to the vaccine. Data are lacking on the vaccine's effectiveness in people of colour, and it is also unknown whether any trial participants developed severe Covid-19. [33] In the case of African countries, their underrepresentation in clinical development of Covid-19 vaccines is proving to be less of a concern than at the outset of the pandemic. The continent has registered lower numbers of infections, hospitalisations and deaths from the disease. While it is not entire clear what explains these outcomes, at least part of the explanation is

that many governments acted early to quarantine those infected. Symptoms associated with mild cases of Covid-19 appeared in Pfizer's phase I trial in more than 50 per cent of the participants, while mild Covid-19-like side effects were associated with Pfizer's and Moderna's vaccine candidates. [34] For some, such symptoms could be worse than what they would experience than if they were naturally exposed to the disease, a phenomenon known as antibody-dependent enhancement (ADE); this was a challenge with experimental vaccines against a cousin of the virus that produces Covid-19, severe acute respiratory syndrome (SARS). [35]

Novavax's candidate, NVX-CoV2373, has two endpoints, which provide greater confidence that it will cover the full range of Covid-19 symptoms:

"The first primary endpoint is first occurrence of PCR-confirmed symptomatic COVID-19 with onset at least 7 days after the second study vaccination in volunteers who have not been previously infected with SARS-CoV-2. The second primary endpoint is first occurrence of PCR-confirmed symptomatic moderate or severe COVID-19 with onset at least 7 days after the second study vaccination in volunteers who have not been previously infected with SARS-CoV-2. The primary efficacy analysis will be an event-driven analysis based on the number of participants with symptomatic or moderate/severe COVID-19 disease. An interim analysis will be performed when 67 per cent of the desired number of these cases has been reached." [36]

While many vaccines focus on efficacy, the most effective ones also stop pathogens from being transmitted, which is as critical as disease prevention; arresting transmission matters, especially during a pandemic. [37] Such vaccines benefit those lacking access, those whose immune systems are already weak and may not respond, those who will experience declining immunity over time, and those who refuse to be vaccinated. [38] The whole population benefits. Despite the value of this standard, most phase III clinical trials focus on reducing the incidence of Covid-19; several trials indicate that incidence of SARS-CoV-2 infections among participants will be assessed only as an ancillary outcome. [39] Interestingly, in the US, the FDA has never granted regulatory approval for vaccines that address just infection prevention; rather, it has focused on evaluating vaccine candidates for disease prevention. The World Health Organisation (WHO) uses assessments of transmission and shedding as endpoints for its phase III clinical trials. Yet the current crop of vaccine candidates are not taking on disease prevention as the main endpoint of their phase III clinical trials. Mainstream immunologists point out the danger in this limited focus:

"With some vaccines, for some diseases, the indirect benefits of vaccination can be greater than the direct effects. Based on these precedents, it could be a grave mistake for vaccine developers now to hew only, or too closely, to the single-minded goal of preventing Covid-19, the disease. Doing so could mean privileging vaccines that don't block the transmission of SARS-CoV-2 at all, or abandoning vaccines that block transmission well enough but that, by prevailing standards, are deemed to not forestall enough the

development of Covid-19. That, in turn, would essentially mean that the only way to ever get rid of SARS-CoV-2 would be near-universal immunization — a herculean task. Focusing on how to block the coronavirus's transmission is a much more efficient approach." [40]

Limitations that may emerge raise the question of what the line is between vaccines and therapeutics. The picture that emerges is that an approved vaccine will not be a silver bullet but simply a tool that is part of a broader set of measures that must continue to be deployed, such as the wearing of masks, good hand hygiene and social distancing – at least until clear and definitive answers to these two pressing issues can be established with evidence over time. Unless the protocols of ongoing phase III trials are amended to take these on, answers will come as any approved vaccine is administered and observations can be made over time.

Apart from the practical concerns about how effective leading vaccine candidates will be is the issue of transparency and the public's right to know more information about the protocols, risks and other issues. These concerns take on a heightened urgency because tax payers' money is behind much of the research and development. Pharmaceutical companies zealously guard many of the specifics of clinical trials until they are finished as these are connected to positioning amid fierce industry competition and protecting intellectual property. However, the unprecedented nature of the pandemic has not obviated the need for quelling legitimate concerns the public has, which have been exacerbated by a vocal anti-vaccination lobby. According to Pew Research Center, "About half of U.S. adults (51 per cent) now say they would definitely or probably get a vaccine to prevent COVID-19 if it were available today; nearly as many (49 per cent) say they definitely or probably *would not* get vaccinated at this time. Intent to get a COVID-19 vaccine has fallen from 72 per cent in May, a 21 percentage point drop. " [41] These findings are broadly consistent across developed countries.

The recent experience of the AstraZeneca/University of Oxford vaccine candidate illustrates the perils in the clinical development process and the need for public information to ensure confidence; phase III clinical trials were stopped twice when two British women became seriously ill with a neurological illness. The University of Oxford, which developed the initial vaccine candidate, posted a document claiming that the illness may not be associated with the virus. While trials have resumed in Brazil, India, South Africa and the UK, it took more time before the US trial resumed.

It is impossible to highlight the pause in the trial without referencing the broader political context in the US, in particular. The public-health institutions in the US had been subjected to immense political pressure by the Trump administration, which was pushing for a public announcement of a vaccine prior to Election Day. Steven Hahn, the head of the Food & Drug Administration (FDA), which has regulatory authority over drugs, stated in late August that he would grant emergency use authorisation (EUA) for Covid-19 vaccine candidates, even without the completion of phase III clinical trials, arguing that the public-health emergency overrides the need for complete assessment of efficacy and safety. Drugs and vaccines are held to a lower medical, legal and scientific standard under EUA, and are linked to the data

that drug companies submit. In the face of public concerns about the lowering of health and safety standards for Covid-19 vaccines, the FDA revised its stance on EUA, pledging to release more rigorous standards that made it impossible for a vaccine to be ready for approval by Election Day.

Credible, mainstream public-health experts and scientists are taking public stances to press companies for more disclosure and for regulatory bodies to maintain rigorous standards of evaluation and assessment. In response to growing public pressure, several drug companies, including Pfizer and AstraZeneca, issued a pledge, committing to be guided not by profit or politics, but by science as the arbiter for evaluating Covid-19 vaccine candidates. Critics pointed out that the pledge did not include a commitment to disclose important research data with independent scientists and the general public, an issue confirmed by the fact that none of these companies have yet to reveal the statistical analysis plans or the protocols for the trials that could help answer some of the issues around efficacy, safety and when a trial could be stopped. [42] The stakes are literally life and death.

The Coalition for Epidemic Preparedness Innovations (CEPI) recently announced the launch of a network of centralised laboratories to centralise assessment of Covid-19 vaccine candidates under phase I and phase IIa clinical development. While the advanced ones are out of reach, this initiative can bring transparency to those in earlier development by allowing for comparability of immunogenicity:

"Typically, the immunogenicity of potential candidate vaccines is assessed through individual laboratory analyses, aiming to determine whether biomarkers of immune response – such as antibodies and T-cell responses – are produced after clinical trial volunteers receive a dose(s) of a vaccine candidate. However, with over 320 vaccine candidates against COVID-19 currently in development, there are likely to be numerous differences in data collection and evaluation methods. This includes potential variation in the range of correlates of immunity being measured by laboratories. Technical differences in how and where samples are collected, transported and stored can also occur, impacting the quality and usefulness of the data produced and making comparisons between measurements in individual laboratories difficult. In addition, with the wide range of COVID-19 vaccine approaches and technologies currently being deployed (e.g., recombinant viral vectors, live attenuated vaccines, recombinant proteins and nucleic acids), standard evaluation of the true potential of these vaccine formulations becomes very complex.

"Through centralising the analysis of samples obtained from trials of COVID-19 vaccine candidates, the new clinical-sample-testing network will minimise variation in results obtained, which could otherwise arise due to such technical differences when carrying out independent analysis. The samples from participating vaccine developers will instead be tested in the same group of laboratories using the same methods, therefore, removing much of the inter-laboratory variability and allowing for head-to-head comparisons of immune responses induced by multiple vaccine candidates." [43]

The initiative is laudable but is only as relevant and useful as the number of pharmaceutical companies that participate.

Manufacturing Capacity, Access and Equity

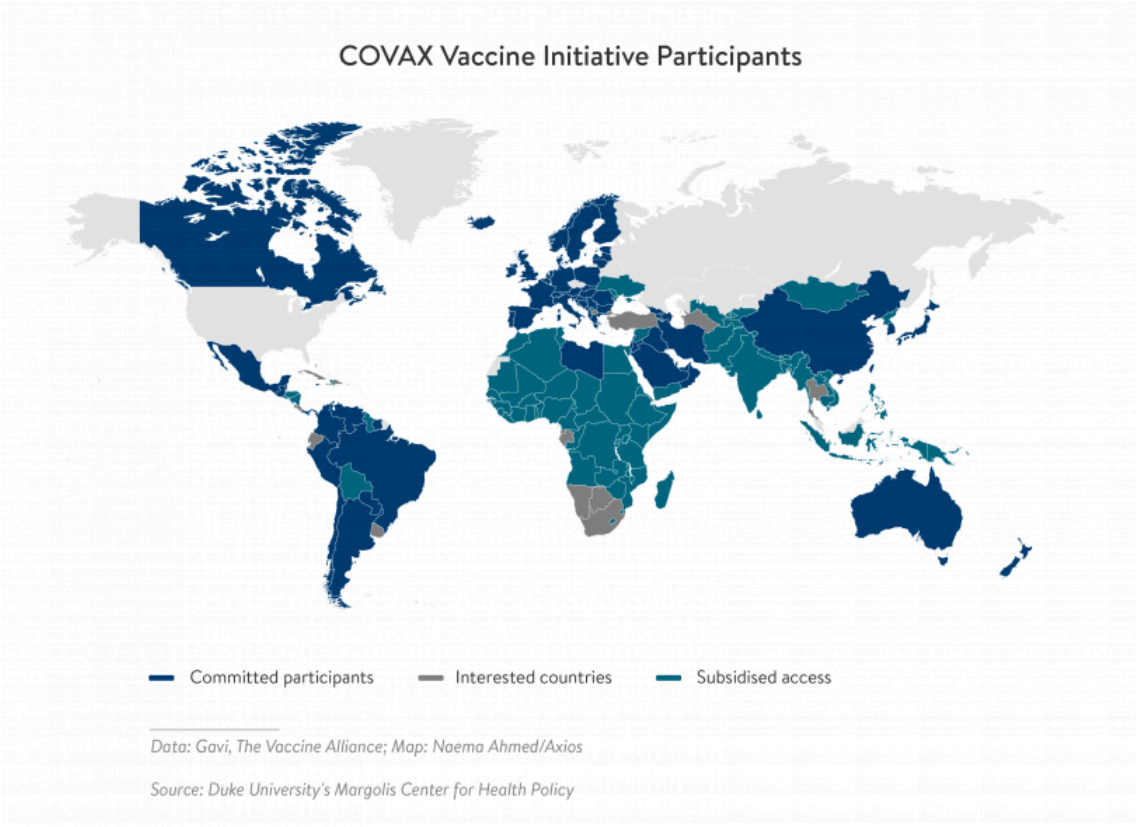
Billions of doses of Covid-19 vaccines will need to be manufactured in order to meet global demand. Currently there is no global coordination of the supply chain, which has contributed to imbalances. To ensure that there would be enough capacity for all countries could be covered, CEPI, PATH, the Clinton Health Access Initiative and the Bill & Melinda Gates Foundation conducted a global survey of vaccine manufacturers to "understand capabilities, capacities and interest in responding to the pandemic. [The collaboration] aimed to assess potential bottlenecks in the vaccine manufacturing and to work out what global capacity might be available to produce billions of doses of vaccine; [the assessment includes] what manufacturing capacity was available to produce drug substance (i.e., the unformulated active [immunogenic] substance) and drug product (i.e., the finished dosage form of the product including final container)." [44] This capacity is not at the expense of other vaccine manufacturing. The underlying concern is about vaccine access for poor countries and to avoid monopolisation of global vaccine supply. For example, the US has acquired access to eight doses per American, assuming all the vaccines in its portfolio make it to market. The good news is that there is enough manufacturing capacity to vaccinate the world's most vulnerable with 2 billion doses by the end of 2020. The bad news, however, is that there is insufficient manufacturing capacity to produce enough doses by that deadline to vaccinate everyone.

COVID-19 Vaccine Global Access (COVAX) is the Covid-19 vaccine-allocation platform facility co-led by the WHO, with the involvement and support from CEPI and Gavi, set up to ensure that low- and middle-income countries are fully included in any research, buying and distribution deals (See Figure 1, which shows the involvement of 171 countries). It offers: doses for at least 20 per cent of countries' population; a diverse and actively managed portfolio of vaccines; delivery of vaccines as they become available; the ending of the pandemic's acute phase; and the means to help economies rebound. [45] The US declined to participate because of its objection to WHO involvement. The Access to COVID-19 Tools (ACT) Accelerator is involved in these efforts, with its vaccines work led by CEPI, Gavi, and the WHO. The UK government, however, recently announced that it would donate USD $735 million to COVAX, with the bulk of that sum for "developing countries to protect themselves." [46] The EU 27 and the Commission are providing COVAX with a tranche of nearly USD $270 million in cash via a European Investment Bank loan, which translates into roughly 88 million doses, to be distributed to low- and middle-income countries; nearly US $200 million in the form of loan guarantees as a contribution from the EU's budget also will be made available. [47] Canadian Prime Minister Justin Trudeau recently pledged USD $220 million to COVAX to earmark the purchase of doses for low- and middle-income countries.

The infusion of funding matters for the recipient countries (see the map in Figure 1 of donor and recipient countries), which has an agreement to supply the equitable and fast global distribution of

approved vaccines to 3 per cent of the population of participating countries. The priorities are people in social-care institutions, high-risk frontline health workers, and weak health systems. Two billion doses will be distributed by the end of 2021. This is supported by nearly USD $1. 5 billion in financial support from individual donors, vaccine manufacturers, governments and a range of organisations. Tranches will be distributed to each country for use in targeted groups until 3 per cent of their population is reached; ultimately however, recipient governments have the final say with respect to how the vaccines are allocated. It is clear that additional funding for COVAX, along with regional and domestic manufacturing deals, will be necessary to provide additional doses to low- and middle-income countries. One avenue for additional coverage is the EU, which has committed to sharing some of its supply with poor countries; it may still be insufficient. While there are clear criteria for access and allocation, it is unclear how execution will occur. In what order will countries receive doses? Moreover, there is no way to guarantee that doses will go to the most vulnerable, raising the possibility that politics may determine access. Science has proved that the pandemic knows no borders. It is in rich countries' interest to support vaccine access for poorer countries.

Figure 1 – Global participants in COVAX



Assuming that a vaccine candidate successfully completes clinical development and is available for public consumption, there will be a range of challenges with respect to access and equity, as vaccine nationalism is a real phenomenon. Lack of global coordination has given rise to go-it-alone approaches to securing

doses for domestic populations. Table 4, included in the Annex, shows the current state of play with respect to the number of doses secured by various countries. The US, through its Operation Warp Speed initiative, is by far the largest funder of vaccine research and buyer of doses. Its USD $10 billion investment supports clinical development and production infrastructure to manufacture doses at scale. To date, the US has acquired 800 million doses with another 1.6 billion doses available as options, which translates to eight doses for every American. [48] That figure is staggering; no other country comes close. In total, Canada has purchased at least 174 million doses from six companies, for a total of USD $1 billion; money for unsuccessful candidates will not be refunded. [49] In late August while Japan was pushing for the Olympics to take place, the government was positioned to purchase 521 million doses in 2021 from five companies for its population of 126 million. [50] The wave of late-phase vaccine candidates is expected to generate a market in 2021 worth USD $20 billion, will be dominated by a small number of players over the next several years, and then fall to between USD $5 billion and USD $6 billion. [51] A vaccine market analysis carried out by Evercore ISI identifies 40 per cent of the Covid-19 vaccine market going to Moderna, with Novavax receiving USD $20 billion. [52]

The key takeaway is that rich countries have ample supply of Covid-19 vaccine doses, which will also assist with economic recovery; poor countries have too few doses. Their fate is much less certain. What is obvious is that economic recovery will continue to be at risk in the absence of an effective vaccine. If rich countries continue to fail to coordinate a global response, then developing countries will necessarily look elsewhere for relief. India holds the potential to address the gap, as it is already a stable supplier of a range of medicines purchased by low- and middle-income countries. China and Russia are also focusing on the developing world with their vaccines. The next section highlights these dynamics.

Geopolitics of Vaccines

It is clear that politics have suffused every aspect of the race to reach a successful Covid-19 vaccine. They are not only domestic but have become international. China and Russia are the only countries to administer their vaccine candidates outside the protocols of phase III clinical trials. China has taken advantage of the pandemic to project itself as a responsible global leader – in contrast to an inward-looking US – providing a range of countries with personal protective equipment (PPE), ventilators, and now, its vaccine candidates that have not completed phase III clinical trials. Its behaviour is also a way to reverse damage done to its international standing; it is the country where the pandemic originated. In a bid to build ties, establish good will, and present itself as a player in the field of science, the Chinese government has made a range of commitments. For example, Latin American and Caribbean countries will have access to USD $1 billion in loans to purchase Chinese-made Covid-19 vaccines, The Philippines will have priority access, and Bangladesh will receive more than 100,000 free doses from Sinovac, a Chinese vaccine maker. [53] The governor of the state of São Paulo, Brazil, signed a contract with Sinovac to receive 46 million doses, with 6 million ready in October and the rest to be manufactured at Brazil's Butantan Institute; the cost per dose has not been disclosed. [54] China's involvement in the COVAX facility changes the politics significantly given its economic and political heft and its commitment to distributing its vaccine candidates to poorer countries. Neither the US nor Russia is involved in the facility. Russia has been aggressive in using its Sputnik V vaccine candidate as a tool of international influence. The government has received requests for more than a billion doses of its unproven vaccine, with preliminary agreements in the Middle East, Asia and South America; Brazil, Mexico, Saudi Arabia and India are in that group. [55] The Russian government announced a deal to supply Egypt with 25 million doses of Sputnik V, via Pharco, one of Russia's leading drug makers; the amount covers 25 per cent of Egypt's population. [56] The EU and the UK have committed to provide support for poorer countries to access vaccines, but it is clearly the case that US absence from global allocation mechanisms has contributed to the Chinese and Russian governments' use of Covid-19 vaccine candidates as tools for political and economic influence.

Bringing the Pandemic Under Control

Political leaders supported by scientific expertise will need to devise and deploy flexible strategies that respond to data on Covid-19 vaccine candidates as they become available. Such real-time data reviews are being deployed in other countries, including Canada and countries in the EU. In addition, once a vaccine is deployed, phase IV surveillance studies will become more important. Ideally, vaccines will be able to provide coverage to most of the population, with therapeutics (antibodies) covering only the most vulnerable who are not candidates for vaccines, including the elderly and those who are immunosuppressed.

The British public longs for a return to a pre-Covid-19 state of being, which is nearly impossible in the absence of a vaccine. Scientific estimates of how much of a given population must be vaccinated to achieve population immunity vary. According to an infectious-disease expert, "In order to get 40 per cent of a population immune through vaccination – if you have a vaccine with 50 per cent efficacy – you're going to have to vaccinate 80 per cent of the population." [57] Vaccines are critical for reducing deaths, hospitalisations and disease severity. Administering the vaccination to the British public will take time and organisation; planning must begin immediately. Government must communicate clearly to the public what a Covid-19 vaccine will and will not do. Ongoing public information campaigns are critical, given the decline in the numbers of people who are committed to being vaccinated. The London School of Hygiene & Tropical Medicine-based Vaccine Confidence Project led research that found that global health is defined not only by vaccines and their efficacy, safety and availability, but also whether the public trusts immunisation. Vaccine hesitancy is a growing phenomenon and has been cited by the WHO as a top 10 threat to global health. Public confidence in immunisation matters for whether vaccines are refused or delayed; these are factors in the increase in the number of disease outbreaks that can be prevented by vaccines, such as meningitis, measles and polio. [58] Misinformation about vaccines is often driven by an unproven safety fear that leads to distrust. Deliberate polarisation of vaccine debates also occurs, and general distrust in science, experts and government influences how the public views vaccines. [59]

As we have argued in our paper, *Light at the End of the Tunnel*, vaccines alone are insufficient to stop the pandemic immediately. Specific interventions such as mass testing and contract tracing, therapeutics (particularly antibody treatments), and robust data collection and management systems will remain necessary. Once vaccination campaigns end, these measures – along with masks and social distancing – may still be necessary if the virus proves to be endemic in the same way that influenza is, though at a much lower level.

On a global level, vaccine nationalism will not abate in the absence of a global, political agreement to guide access for poor countries. Not every vaccine candidate is suited to every country; capacity to administer will depend in part on infrastructure, some of which may not be available. Finally, insufficient coverage for poor countries may undermine efforts to stop the pandemic. Doing so will require coordinated political leadership, greater transparency from drug companies, more widespread uptake and a better educated public.

Annex

Table 1 – Covid-19 vaccines under clinical development

Players	Stage	Manufacturing Process	Approach	Country	Capacity/ Collaboration for Access
Moderna	Phase III trials	Nucleic acid synthesis	RNA	US	Tech transfer to Lonza plants in Switzerland and the US is due to start in June, with production scheduled for July. Some CEPI money.
Vaccitech, University of Oxford/Astra Zeneca (AZD1222, formerly ChAdOx1 nCoV-19)	Phase III trials	Biomanufacturing	Non-replicating viral vector	UK	Partnered with CMOs Halix (NL), Cobra, and Oxford Biomedical for initial manufacturing. Collaborating with AZ for global distribution.

					Millions of doses could be available by September. Wuxi and SRI are reportedly also getting rights. Intelligence suggest collaborating with Janssen.
Inovio Pharmaceuticals	Phase I/II trials (on partial hold until it responds to FDA questions about the trial and the delivery device that will be used.	Nucleic acid synthesis	DNA	US	Inovio has a lawsuit pending against manufacturer, VGXI.
Applied DNA and Takis Bio (for use in felines)	Starting clinical trials in autumn	Nucleic acid synthesis	DNA	US / Italy	Applied DNA began large-scale production of five vaccine candidates, using

					the company's proprietary PCR-based DNA ("LinearDNA") manufacturing systems.
Sinovac Biotech	Phase III trials	Biomanufacturing	Inactivated virus	China	Sinovac will produce up to 100 million doses of CoronaVac each year.
CanSino Biologics and Beijing Institute of Biotechnology, Academy of Military Medical Science	Phase III	Biomanufacturing	Non-replicating viral vector	China	Petrovax will produce the vaccine once it is registered by the Russian Federation.
Wuhan Inst. of Biological Products and Sinopharm	Phase III	Biomanufacturing	Inactivated Virus	China	CNBG (Sinopharm's subsidiary) will manufacture 200 million doses a year at two new vaccine production facilities in Beijing and Wuhan.

Beijing Institute of Biological Products, China National Pharmaceutical Group (Sinopharm)	Phase I/II	Biomanufacturing	Inactivated Virus	China	Sinopharm has two new production facilities, built with a USD$300 million investment that can produce 220 million doses each year. They are in Beijing and Wuhan.
Gamaleya Research Institute, Acellana Contract Drug Research and Development	Phase III	Biomanufacturing	Non-replicating viral vector	Russia	Gamaleya and Sistema's pharmaceutical plant are manufacturing in Russia
Novavax, Emergent Biosolutions, Praha Vaccines, Biofabri, Fujifilm Diosynth Biotechnologies, FDB, Serum Institute of India, SK Bioscience, Takeda Pharmaceutical Company, Limited, AGC Biolgoics,	Phase III	Biomanufacturing	Protein	US	$388m in funding from CEPI to boost manufacturing. In June 2020, US Department of Defense (DoD)provided a $60 million contract to Novavax to manufacture in June 2020.

Polypeptide Group, **Endo**	Novavax will supply 10 million doses to the DoD in 2020 to be used in phase II/III clinical trials or under an Emergency Use Authorisation, ifapproved. Agreement with Serum Institute of India to manufacture the antigen component of NVX-CoV2373, increasing production capacity to over 2 billion doses per year. Endo's Par's generics unit produce bulk batches of Novavax's candidate for a pivotal late-stage clinical trial and then handle commercial finishing duties if the vaccine gets approved.

University of Melbourne; Murdoch Children's Research Institute	Phase II/ III	Biomanufacturing	Live attenuated virus	Australia	Unknown
Pfizer and BioNTech	Phase II/ III trials	Nucleic acid synthesis	RNA	UK	Pfizer is manufacturing in the US and Europe. BioNTech has agreed to buy a biologics facility in Germany. It will be operational by Q2 2021 with annual capacity of up to 750 million doses.
J&J (Janssen) JNJ-78436735	Phase III	Biomanufacturing	Non-replicating viral vector	Belgium	With BARDA's support, Janssen will scale up to produce up to 300 million doses of vaccine in the US each year. J&J is partnering with Emergent BioSolutions to add manufacturing capacity to its own efforts.

Bharat Biotech; National Institute of Virology	Phase III	Biomanufacturing	Inactivated virus	India	Manufactured in Bharat Biotech's BSL-3 (Bio-Safety Level 3) high containment facility.
Arcturus Therapeutics and Duke-NUS Medical School	Phase I/II		Self-replicating RNA	US/ Singapore	Partnership will combine Arcturus' low-dose STARR™ mRNA vaccine technology with Catalent's scalable cGMP manufacturing capabilities to produce millions of doses of LUNAR-COV19 mRNA in 2020 and potentially 100s of millions of doses annually for worldwide use.
Zydus Cadila	Phase II	Nucleic acid synthesis	DNA	India	In-house manufacturing
Takara Bio, AnGes, Japan Agency for	Phase I/II	Nucleic acid synthesis	DNA	Japan	Partnership with Osaka University

Medical Research and Development					and AnGes Co., Ltd. to manufacture doses
Genexine	Phase I/II	Nucleic acid synthesis	DNA	South Korea	Binex is the contract manufacturer
Symvivo	Phase I trials	Biomanufacturing	Other	Canada	In-house manufacturing
Research Institute for Biological Safety Problems, Republic of Kazakhstan	Phase I/II	Biomanufacturing	Inactivated	Kazakhstan	Unknown
Anhui Zhifei Longcom Biopharmaceutical, Institute of Micbrobiology of the Chinese Academy of Science	Phase II trials	Biomanufacturing	Protein	China	Unknown
CureVac	Phase II	Nucleic acid synthesis	RNA	Germany	The company is prepared to manufacture

					several hundred million doses per year at its facility in Germany. The Bill & Melinda Gates Foundation has provided USD$52 million to build out production facility. 100 million doses will be produced by the end of 2020
Adimmune	Phase I	Biomanufacturing	Protein	Taiwan	JHL Biotech will manufacture the vaccine
Imperial College London	Phase I/II	Nucleic acid synthesis	RNA	UK	$8.4M funding from CEPI. Imperial's supply chain and manufacturing partners will be ready to produce tens of millions of vaccines starting in early 2021.

Vector Institute	Phase I/ II, but already registered	Biomanufacturing	Protein	Russia	Possible collaboration with Biocad to produce in China
Vaxine Pty Ltd, Flinders University, Oracle, Medytox, Sypharma, Oxford Expressions Technology	Phase I	Biomanufacturing	Protein	Australia	Under a future agreement Mabion SA would lead clinical development, manufacturing, regulatory negotiations and could exclusively market the vaccine in the EU and – optionally – in the US.
West China Hospital, Sichuan University	Phase I	Biomanufacturing	Protein	China	Unknown
ReiThera, Leukocare; Univercells	Phase I	Biomanufacturing	Non-replicating viral vector	Italy	Univercells' bioproduction platform will be used for ultra-fast ramping up of GMP manufacturing

Medicago, GSK, Dynavax	Phase I	Greenhouse production	Plant-based adjuvant	Canada	Partnership will use Medicago's plant-based facilities manufacture approximately 100m doses by the end of 2021. By the end of 2023, a large-scale facility under construction in Quebec City, Canada, expected to deliver up to 1 billion doses annually.
CSL, University of Queensland	Phase I	Biomanufacturing	Protein	Australia	Unknown
COVAX/ University of Nebraska Medical Center, DASA	Phase I	Biomanufacturing	Protein	USA	COVAX will manufacture internal components and partner for fill and finish.
Instituto Finlay de Vacunas	Phase I/II	Biomanufacturing	Protein	Cuba	Under discussion with Cuban companies

Clover Biopharmaceuticals, GSK, Dynavax	Phase I	Biomanufacturing	Protein	Australia	GSK manufacturing
Federal Budgetary Research Institution (FBRI) State Research Center of Virology and Biotechnology "Vector"	Phase I/II but already registered	Biomanufacturing	Protein	Russia	Unknown
Merck; IAVI	Phase I	Biomanufacturing	Recombinant	US	In-house manufacturing
Vaxart	Phase I	Biomanufacturing	Protein	US	MOU with Atwill Medical Solutions (AMS) for large-scale manufacturing.
University of Pittsburgh Center for Vaccine Research	Phase I	Biomanufacturing	Measles vector	US	Themis Bioscience will manufacture the vaccine
Sanofi, Pasteur, GSK	Phase I/II	Biomanufacturing	Protein	France / UK	in-house manufacturing

Beijing Wantai Biological Pharmacy Enterprise with researchers from Xiamen University and Hong Kong University	Phase I	Biomanufacturing	Attenuated virus (intra-nsasal)	China	Unknown

Table 2 – Covid-19 vaccine candidates: doses, storage temperatures, availability and cost

Company	Vaccine Name	Number of Doses	Storage Temp	Estimated Availability	Cost
Moderna	mRNA-1273	2	-4°F	Emergency use authorisation after 25 November and final approval likely in late January	USD $32-USD $37 per dose (priced for a return)
AstraZeneca/ University of Oxford	AZD1222	2	*2*°C to *8*°C	Possibly by the end of 2020	USD$4 per injection (not priced for profit during the first phase of the pandemic)

Sinovac Biotech	CoronaVac	2 shots	*2°C to 8°C*	Now	USD $60 for two shots in select Chinese cities
CanSino	Ad5-nCoV	2	*2°C to 8°C*	Approved for use by the military on June 25 for a period of one year	Undisclosed
Beijing Institute of Biological Products, China National Pharmaceutical Group (Sinopharm)	Unknown	2	*2°C to 8°C*	November/ December 2020	USD $150
University of Melbourne; Murdoch Children's Research Institute	BCG	1 shot	+2°C and +8°C. It is even more stable if stored in temperatures as low as -20°C	Not at least until after March 2020, when phase III clinical trial will end	USD $2- $3 per dose
BioNTech and Pfizer	BNT162	2 shots	-94°F	Applying for emergency use	USD $19.50

				authorisation in November and, if regulatory authorisation or approval is obtained, currently plan to supply up to 100 million doses worldwide by the end of 2020 and around 1.3 billion doses by the end of 2021.	
Johnson & Johnson/ Janssen	Ad26.COV2.S	1 shot	Shipped frozen, but can be stored in liquid form at refrigerator temperatures for three months	Phase III data by the end of 2020	USD $10 per dose (not priced for profit during the first phase in the pandemic)
Sinopharm/ Wuhan Institute of Biological Products	2019-nCov Inactivated Vaccine	2 shots	*2°C to 8°C*	In widespread use in China now; approval expected end of December 2020	Just under USD $145 for two doses

Sanofi/GSK		2 shots	Shipped in liquid form and can be stored at refrigerator temperatures, between 2°C and 8°C	First half of 2021	Just under USD $12
Novavax	NVX-CoV2373	2 shots	Handling in an unfrozen, liquid formulation that can be stored at 2°C to 8°C	As early as late 2020	About USD $16 per dose
Vector Institute	EpiVacCorona	2 shots	2°C to 8°C	Already registered	Undisclosed
Gamaleya Instiute	Sputnik V	2 shots	2°C to 8°C	Already registered and in widespread use with mass circulation in October, Phase III trials under way	Undisclosed
Sinovac	CoronaVac	2	Could remain stable for up to three years in storage; extrapolated from data vaccines	Already in widespread use	USD $29.75 per dose

			readings stayed within acceptable ranges for 42 days at 25°C (77°F), 28 days at 37°C (98.6° F), and five months for 2° to 8°C (35.6° to 46.4°F) [60]		
CureVac	Unknown	2 shots	Tests are underway to show that it can be stored for months at refrigerator temperatures	May seek approval in 2021	Company will seek "an ethical margin" on price
Valneva	VLA2001	2 shots	*2°C to 8°C*	Potential regulatory approval in the second half of 2021	Undisclosed

Table 3 – Characteristics of ongoing phase III Covid-19 vaccine trials [61]

	Moderna	**Pfizer**	**AstraZeneca (US)**	**AstraZeneca (UK)**	**Janssen**	**Sinopharm***	**Sinovac**

Vaccine name	mRNA-1273	BNT162	AZ01222	AZD01222	Ad26COV25	Sinopharm vaccine	Sinovac CoronaVac
Target enrolment	30,000	43,998	30,000	19,330	60,000	45,000	8,870
Ages eligible	18+	12+	18+	5-12, 18+	18+	18+	18+
Protocol publicly available	Y	Y	Y	N†	Y	N	N
Notable excluded populations							
Children and adolescents	Excluded	Many excluded	Excluded	13-17 excluded	Excluded	Excluded	Excluded
Immuno-compromised patients	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
Pregnant or breastfeeding women	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded

Endpoints undergoing formal study‡							
Prevention of symptomatic disease in vaccine recipient	Y	Y	Y	Y	Y	Presumably§	Y
Reduction in severe Covid-19 (hospital admission, ICU or death)	N	N	N	N¶	N	N	N
Interruption of transmission (person-to-person spread)	N	N	N	N	N	N	N

*This trial is separately randomising an inactivated SARS-CoV-2 vaccine (Vero cell) manufactured by Wuhan Institute of Biological Products Co and Beijing Institute of Biological Products Co.

† AstraZeneca has released the protocol for its stalled US trial but not its trial in UK, Brazil, and South Africa.

‡ Endpoints "undergoing formal study" include those listed as primary outcomes in ClinicalTrials.gov, publicly available study protocols, or those not listed as primary outcomes, but the company has confirmed that the study is powered sufficiently to find an effect (if one exists).

§ Sinopharm lists "incidence of COVID-19 cases" as a primary efficacy endpoint in its ClinicalTrials.gov entry.

¶ Trial registration (NCT04444674) lists the following primary endpoint: "Determine if there is a reduction of severe and non-severe COVID-19 disease in HIV-negative adults." This suggests a composite outcome that includes non-severe disease.

Table 4 – Doses of Covid-19 vaccine candidates secured by various governments

Company	Target Country	Doses	Cost
Sanofi, GSK	EU	Up to 300 million doses with some diverted to low- and middle-income countries	USD$11.68/dose, approximately USD$3.5 billion
Pfizer, BioNTech	EU	200 million doses with an option to purchase an additional 100 million doses	Undisclosed
Moderna	EU	80 million doses, with an option to purchase an additional 80 million doses	Approximately USD $1.24 billion
CureVac	EU	225 million doses with an option to purchase an additional	Undisclosed

		180 million doses (will allow EU to provide donations to low- and middle-income countries)	
AstraZeneca and University of Oxford	EU	400 million doses	$2.92 per dose, approximately USD $1.17 billion
Johnson &Johnson	EU	200 million doses with an option to purchase an additional 200 million doses	Undisclosed
Sanofi, GSK	Canada	72 million doses	Government has allocated USD $1 billion for all doses
Pfizer	Canada	20 million doses with the option to purchase additional doses (quantity unknown)	Government has allocated USD $1 billion for all doses
AstraZeneca and University of Oxford	Canada	20 million doses	Government has allocated USD $1 billion for all doses
Moderna	Canada	56 million doses	Government has allocated USD $1 billion for all doses

Novavax	Canada	76 million doses	Government has allocated USD $1 billion for all doses
Johnson & Johnson/ Janssen	Canada	38 million doses	Government has allocated USD $1 billion for all doses
COVAX	Canada	15 million	USD $165 million
Sanofi, GSK	UK	60 million doses	Undisclosed
BioNTech, Pfizer	US	40 million doses	Undisclosed
Astra Zeneca/ University of Oxford	UK	100 million doses	Undisclosed
Novavax	UK	60 million doses	Undisclosed
Valneva	UK	60 million doses; two further options for additional doses—one for 40 million and the other, between 30 million and 90 million—by 2025	USD $1.6 billion

J&J/Janssen	UK	30 million doses, with an option for an additional 22 million doses	Undisclosed
Pfizer and BioNTech	US	Up to 100 million doses	$2 billion
Sanofi/GSK	US	100 million doses with an option to purchase an additional 500 million doses	US government to pay up to $2.1 billion to support further development of the vaccine including clinical trials, and the manufacturing scale-up and delivery of the initial 100 million doses
AstraZeneca and University of Oxford	US	300 million doses	USD $1 billion
Moderna	US	100 million doses	$1.5 billion
J&J/Janssen	US	100 million doses	USD $1.5 billion
AstraZeneca	Brazil	100 million doses	$360 million
Moderna	Japan	40 million doses	Undisclosed

Pfizer Inc and BioNTech	Japan	120 million doses	Undisclosed
AstraZeneca	Japan	30 million doses, and up to120 million dose	Undisclosed
AnGes	Japan	1 million doses	Undisclosed
Johnson & Johnson	Japan	undisclosed	undisclosed
Novavax, with a license to Takeda for local production	Japan	Up to 250 million doses	Undisclosed
AstraZeneca	Australia	33.8 million doses	$1.24 billion for both AstraZeneca and University of Queensland/CSL
University of Queensland/ CSL	Australia	51 million doses	$1.24 billion for both AstraZeneca and University of Queensland/CSL

Footnotes

1. ^ Pfizer press release, "Update: Alberto Bourla discusses Covid-19 vaccine efficacy results," Pfizer corporate website, 9 November 2020, available online at https://www.pfizer.co.uk/update-albert-bourla-discusses-covid-19-vaccine-efficacy-results
2. ^ Efficacy is assessed as prevention of virologically confirmed disease.
3. ^ Ewen Callaway, "The coronavirus is mutating – does it matter? Nature, 8 September 2020, available online at https://www.nature.com/articles/d41586-020-02544-6: "A typical SARS-CoV-2 virus accumulates only two single-letter mutations per month in its genome – a rate of change about half that of influenza and one-quarter that of HIV."
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7. ^ Department of Health and Social Care, "Independent Report: JCVI: updated interim advice on priority groups for Covid-19 vaccination," 25 September 2020, available online at https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-25-september-2020/jcvi-updated-interim-advice-on-priority-groups-for-covid-19-vaccination#fnref:2
8. ^ Barry R. Bloom, Ph.D., Glen J. Nowak, Ph.D., and Walter Orenstein, M.D, "When will we have a vaccine? Understanding questions and answers about Covid-19 vaccination," New England Journal of Medicine, 8 September 2020, available online at https://www.nejm.org/doi/full/10.1056/NEJMp2025331
9. ^ London School of Hygiene & Tropical Medicine, "Largest global vaccine confidence survey reveals hesitancy hotspots," 10 September 2020, available online at https://www.lshtm.ac.uk/newsevents/news/2020/largest-global-vaccine-confidence-survey-reveals-hesitancy-hotspots
10. ^ Covid vaccine tracker, London School of Hygiene & Tropical Medicine, available online at https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/
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