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are already facing manufacturing delays. These delays are creating chaos for many national vaccination programmes, leading to calls for coordinated efforts by governments and manufacturers to increase production.[1]

These pharmaceutical companies have benefited greatly from huge sums of public funding for research and development and advance purchase commitments, amounting to between US$2·2 billion and $4·1 billion (by Feb 1, 2021) from Germany, the UK, and North America combined (appendix). Yet unfortunately, these governments did not make their support conditional on measures that would enable more vaccine to be produced through, for example, patent pools (eg, the COVID-19 Technology Access Pool) or non-exclusive licensing, which would allow pharmaceutical companies with spare manufacturing capacity to increase supply. So far, most effort has gone into increasing production capacity in the vaccine developers' own facilities or through subcontracts and licensing arrangements with other developers, such as AstraZeneca's agreement with the Serum Institute of India, or Sanofi's support in filling and packing bottles of Pfizer–BioNTech's vaccine.

It is not, however, too late to take bold measures to increase production. Ideally, an agreement could be reached with the patent holders to make the relevant intellectual property available. However, if this agreement is not possible, compulsory licensing is possible (ie, when a government grants permission to someone else to produce a patented product).[2] Compulsory licensing is permitted in exceptional circumstances: public health emergencies,[3] such as the COVID-19 pandemic.

Together, thirteen EU member states account for more than 60% of the world's major facilities for vaccine production and 90% of global vaccine production.[4] Of course, changes would be needed to refocus production to COVID-19 vaccines, but this approach could boost production in the immediate future. It would also enable vaccine manufacturers in low-income regions to start producing immediately,[5] especially benefiting those countries that are far down the list to receive vaccines. Delays in vaccine production and deployment will lead to avoidable morbidity, mortality, and repeated lockdowns with detrimental health, social, and economic consequences that are related to COVID-19. Effective and coordinated roll-out plans are urgently required to speed up deployment of existing vaccines. The EU should also use all instruments that are available, including compulsory licensing, to overcome the delays in vaccine production and to protect public health in this unprecedented crisis.

Throughout the pandemic, things that were once considered to be impossible, such as lockdowns and other severe restrictions on personal and economic liberty, have become accepted. There is no reason why our approach to vaccine development and manufacture should be any different.

We declare no competing interests.

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Guidelines should not pool evidence from uncomplicated and severe COVID-19

The WHO Global Development Group guidelines on COVID-19 therapeutics are meant to provide evidence-based advice to all countries on the medical management of patients with COVID-19.[1,2] The only small-molecule drug to show unequivocal benefit to date is dexamethasone. In the largest randomised controlled trial in patients who were admitted to hospital with COVID-19 (ie, the RECOVERY trial), dexamethasone at a low dose reduced mortality in the prospectively defined subgroups of patients requiring medical oxygen (rate ratio 0·82 [95% CI 0·72–0·94]) or being ventilated (0·64 [0·51–0·81]) but not in patients not receiving respiratory support at randomisation (1·19 [0·91–1·55]).[3] The current WHO living guideline on COVID-19 therapeutics[1] recognises this important difference in therapeutic response in relation to stage of the disease by recommending use of corticosteroids in patients requiring respiratory support but conditionally recommending against their use in patients not requiring respiratory support. By stark contrast, largely on the basis of inpatient studies, the guideline has recommended strongly against hydroxychloroquine (87·4% [9549 of 10 921] of studied patients were inpatients[1]) and lopinavir–ritonavir (all 7429 patients were inpatients[1]) in patients with any disease severity. There is convincing evidence that these drugs do not

benefit patients who are admitted to hospital and, outside hospitals, they should be used only in the context of clinical trials. However, on the basis of our current understanding of the evolution of COVID-19 (appendix), this broad generalisation from the treatment of severely ill patients who have been admitted to hospital to patients with uncomplicated COVID-19 in the community is not supported by current evidence. COVID-19 reflects a changing pathological process. Viral burden peaks early, around the time of first symptoms. This timepoint is when antiviral drugs are likely to be most beneficial. Thereafter, viral burden declines and inflammatory processes dominate in those patients who deteriorate and require admission to hospital, and ultimately respiratory support. Immune modulators and anti-inflammatories are more likely to be of benefit at this later stage but might be harmful if used earlier (ie, by enhancing viral replication).[2] Evidence reviews[2] and the guidelines that they generate[1] should recognise that, although SARS-CoV-2 is one virus, both the COVID-19 disease process and access to health care vary widely. The WHO Global Development Group "prioritized outcomes taking a patient perspective".[2] They decided that mortality would be most important to patients, followed by need for and duration of mechanical ventilation. We argue that prevention of hospital admission is the therapeutic priority for low-resource settings, which usually have few facilities for intensive care. Efficacy assessments in prevention and in uncomplicated COVID-19 should not be pooled with results from severely ill patients who have been admitted to hospital.

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Vaccines and SARS-CoV-2 variants: the urgent need for a correlate of protection

Immune-escape variants have raised concerns about the effectiveness of vaccines as the world scales up SARS-CoV-2 immunisation. COVID-19 vaccines have shown up to 95% efficacy[1] in preventing clinical cases and up to 100% efficacy[2] in preventing severe disease or admission to hospital in settings with pre-existing variants. New variants, especially 501Y.V2 (B.1.351), which escape natural-induced and vaccine-induced immunity, have created uncertainty on whether the vaccines are effective in preventing both mild and severe COVID-19.

Preliminary reports show that the 501Y.V2 variant has complete immune-escape in South African convalescent serum samples,[3] and reductions in neutralising activity in vaccinee serum samples for all four vaccines tested.[4–7] Although these reductions were small for the BBIBP-CorV,[4] BNT162b2,[5] and mRNA-1273[6] vaccines, preliminary data suggest they were substantial, including with a complete immune escape for the AZD1222 vaccine.[7] Concerningly, the clinical trial efficacy of AZD1222 was 70% in the UK and Brazil,[8] but 22% according to preliminary data from South Africa.[7] For NVX-CoV237 the efficacy was 89% in the UK but 49% in South Africa,[9] whereas for Ad26.COV2-S the efficacy was 72% in the USA but 57% in South Africa.[10] Extrapolating vaccine efficacy against pre-existing variants to new variants could be seriously misleading.

Adequate genomic surveillance, standardised variant nomenclature, and a repository of variants and vaccinee serum samples[11] are needed to deal with the challenges of repeatedly emerging new SARS-CoV-2 variants, but there is a particularly pressing need to establish a correlate of protection so that vaccine efficacy results obtained with pre-existing variants can be translated to newly emerging variants because it is impractical and time consuming to repeat clinical trials with each new immune-escape variant. Furthermore, repeating clinical trials for each variant might take so long that even newer variants could emerge while these clinical trials are underway.

Because the immune responses required to prevent mild disease might be different to severe disease, correlates of protection might need to be stratified on the basis of disease severity. There are four key requirements to achieve this aim. First, all SARS-CoV-2 vaccine developers with existing or completed efficacy trials should commit to transparency and open data sharing. Second, an expert committee (preferably under WHO) should be appointed to review existing and planned analyses to identify correlates of protection for each efficacious vaccine. Third, studies with multiple vaccines to fast-track the identification of an animal model, assay, or marker as a correlate of protection should be initiated to address gaps in the correlate research plans. Finally, a central database should be created to collate data for each of the efficacious vaccines, thereby providing larger sample sizes to assess multiple variables as correlates of protection and to test if a correlate identified in one trial is valid in other trials.

The identification of a correlate of protection is too important and urgent

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