

EDITORIALS



Addressing Vaccine Inequity — Covid-19 Vaccines as a Global Public Good

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The first peer-reviewed clinical trial evidence that a Covid-19 vaccine provided robust protection against SARS-CoV-2 infection was published in the *Journal* in December 2020,¹ less than a year after the sequence of the viral genome was reported. This unprecedentedly rapid development of vaccines was a scientific triumph. In the year since, about 62% of the world's population has received at least one dose of a Covid-19 vaccine, and 54% have completed the primary vaccine series.² This would appear to be a landmark success in global health mobilization.

The truth, of course, is very different. The availability of Covid-19 vaccines differs vastly across the globe (Fig. 1). While several wealthy countries have exceeded 90% vaccine coverage, only about 11% of all people in low-income countries have received at least one dose, and only 25% of our health care colleagues in Africa were fully vaccinated by November, before the omicron wave.³ Approximately three billion people worldwide have not received a single dose. The gulf in vaccination rates according to national income is overwhelming, despite the fact that a number of the pivotal phase 3 trials that led to vaccine licensing were conducted in part in some less developed countries. Poorer countries with no capacity to manufacture vaccines joined the end of the queue, as countries with manufacturing capacity prioritized local supply and wealthier countries purchased the vaccines. We should not be surprised by vaccine nationalism; company CEOs and boards have a fiduciary

responsibility to maximize their stock price, and politicians are elected to prefer the interests of their voters over populations in other nations, despite cogent arguments to prioritize vaccinations globally for the vulnerable and for health care workers.⁴

And a new challenge to the global vaccine supply has emerged: data from multiple in vitro and real-world studies published in the *Journal* have shown that antibodies to SARS-CoV-2 wane over a matter of months after vaccination, findings that underscore the need for a booster to restore high antibody levels both to reduce infection with new variants and to minimize hospitalization and death.⁵ In developed countries, the rapid emergence of the omicron variant has increased the urgency of these booster doses. Israel, a front-runner in providing booster doses, is now testing the efficacy of yet a fourth vaccine dose, and further boosters and redesigned vaccines are likely to be needed over time. These developments guarantee that existing vaccine supplies will be directed to rich countries, further delaying their availability in poor countries. Appeals from the World Health Organization (WHO) to delay booster doses in order to prioritize first doses to the world's three billion unvaccinated people have gone unheeded in countries that see boosters as the way to open their economies and end unpopular social interventions. There is also the risk that "old vaccines" will be dumped on poorer countries as the rich shift to second-generation redesigned vaccines.

The COVAX (Covid-19 Vaccines Global Access) program, set up as part of the ACT (Access to Covid-19 Tools) Accelerator and led by GAVI (the Vaccine Alliance), CEPI (the Coalition for Epidemic Preparedness Innovations), and the WHO to support equitable access, was established in anticipation of this problem. But COVAX's impact has been muted by supply-chain issues, vaccine nationalism, the decision by some countries to halt the export of vaccines, and queue-jumping by wealthy countries, which caused its initial projections of vaccine availability to be cut substantially.⁶ The two largest countries in the world, China and India, improved the situation by vaccinating their populations through their national production. But the majority of countries have no local production capacity and are entirely dependent on external purchases, vaccine diplomacy, or donations. Developed countries that send about-to-expire batches of vaccine to poorer countries do little to address inequities.

Furthermore, different vaccines have different efficacy against illness, and the half-life of that efficacy, along with supply, would ideally be factored into any global vaccination strategy, but this cannot happen when the different vaccines vary in price and availability. Fortunately, even one dose of most vaccines appears to adequately boost those who have had a primary infection, which suggests that even a single vaccination may be a beneficial bridge to completing a primary series in countries where the prevalence of antibodies due to primary infection is high.

It has become an article of faith that “no one is safe until everyone is safe,”⁷ but in countries that can vaccinate a very high proportion of their populations and supply boosters, and perhaps boosters-on-boosters, Covid-19 may become a controllable infection (although the emergence of immune-escape variants remains an ever-present threat and immunosuppressed people remain at risk). In countries with low vaccine coverage, however, SARS-CoV-2 will still cause major morbidity and mortality, strain health systems, sicken health workers, and cause economic disruption and will potentially provoke intermittent travel bans when new variants emerge. As developed countries stockpile boosters in response to virus variants, when will less-developed countries find a timely and secure supply of Covid-19 vaccines?

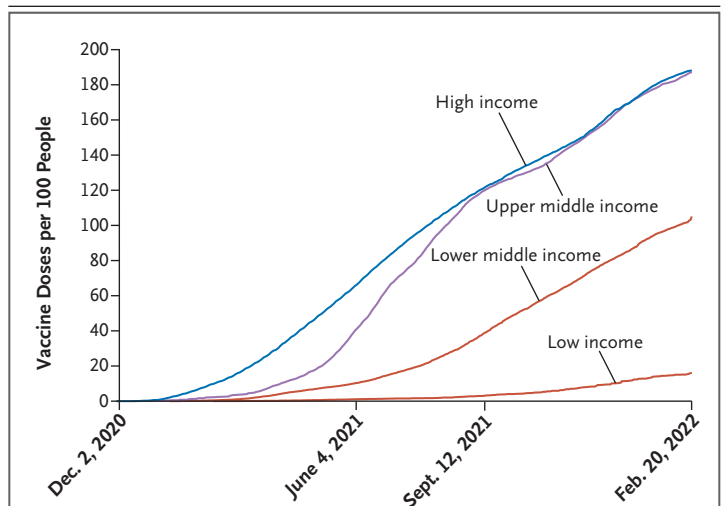


Figure 1. Covid-19 Vaccine Doses Administered in Countries Categorized by Income Level, December 2, 2020, through February 20, 2022.

Income categories are those defined by the World Bank. All doses, including boosters, are counted individually; since the same person may receive more than one dose, the number of doses may exceed the number of people in the population. Data are from Our World in Data (<https://ourworldindata.org/covid-vaccinations>).

It is argued that the self-interest of rich countries should lead them to help vaccinate poorer countries because the uncontrolled spread of SARS-CoV-2 could foster the emergence of escape mutants that will unsettle their vaccine-induced protection against infection, hospitalization, and death. But although such unchecked viral replication and transmission increase the risk of new variants, SARS-CoV-2 evolution in immunosuppressed patients can create new variants anywhere, including the developed world.⁸ Since current vaccines do not provide sterilizing immunity against infection with new variants such as omicron, SARS-CoV-2 will continue to circulate, and perhaps mutate, even in highly vaccinated populations. The case for global vaccine equity cannot rest solely on a defense against escape mutants. Morality and social justice argue that Covid-19 morbidity and mortality and their impact on economic and health systems should be prevented in all countries, rich and poor, around the world.

In the short term, poorer countries will have to compete for the purchase of vaccines in the global marketplace and hope that the COVAX

mechanism can radically speed up and augment deliveries, despite the COVAX CEO's assessment that "what we do not have today are the resources to help countries adapt to the new challenges that we know Covid-19 will create in 2022."⁹ Meanwhile, one potential solution, a World Trade Organization TRIPS waiver of intellectual property rights due to a public health emergency, has been stymied for over 18 months, despite endorsements from the WHO, the U.S. president, and over 100 governments,¹⁰ including those of India, South Africa, Russia, and China. The Oxford–AstraZeneca ChAdOx1-nCoV-19 vaccine and some others have been voluntarily licensed to multiple countries for scaled-up production. Baylor College of Medicine has made publicly available the formula for a protein subunit vaccine that has received Emergency Use Authorization in India.¹¹ But the mRNA vaccine strategy that can most flexibly accommodate antigenic changes remains fiercely protected by the companies involved, despite being based on research funded for decades from the public purse. In the early months of vaccine production, the argument that supply chains for the 280 ingredients necessary for mRNA vaccine manufacture would be disrupted by any change might have made sense. But continuing exclusivity has meant that little public funding has gone into scaling up the production of those ingredients, a situation that perpetuates these limitations in the supply chains. It is long past time to break this impasse.

The medium-to-long-term solution is clear. Less developed and smaller countries need access to local or regional capacity to manufacture vaccines, because they cannot rely on the excess production capacity of richer countries for vaccine supplies in this or future pandemics. A report in 2017 estimated that over 99% of the vaccines used in Africa were imported, and astonishingly, although in 1997 about 55 countries had vaccine manufacturing capacity, by 2015 commercial and regulatory pressures had reduced that number to fewer than 20.¹² This situation contrasts with aims of the Global Action Plan for influenza vaccines developed by the WHO, which has emphasized and supported regional manufacture of flu vaccines.¹³ CEPI plans to develop an international network that will reduce the time needed to produce a vaccine

against a new epidemic pathogen to 100 days,¹⁴ but the immediate test case is how to ramp up the production of the most effective Covid-19 vaccines today.

A sustained effort to develop and increase regional vaccine-production capacity is needed to reduce reliance on the business plans of a handful of commercial entities. This should include licensing and technology transfer arrangements such as those developed by the WHO and the Medicines Patent Pool, which have successfully made antiretroviral treatments widely and cheaply available to treat AIDS, even in the poorest countries. The WHO has gone further, creating vaccine hubs, such as the mRNA vaccine hubs in South Africa and five other African countries,¹⁵ that hold the promise of locally developed and manufactured vaccines for Covid-19 and future pandemics. The chair of the International Monetary Fund maintains that financing vaccine production in Africa is "good for the world," since the investment needed is tiny as compared with the global economic impact of Covid-19.¹⁶ An alternative, giving poor countries loans to purchase Covid-19 vaccines, only perpetuates indebtedness. Finally, as new vaccines are developed, regulatory mechanisms must adapt to changing circumstances; where a high proportion of people have partial immunity from natural infection, vaccination, or both, phase 3 trials that aim to show the superiority of a new Covid-19 vaccine become impossibly large, making noninferiority studies the preferred option in order to increase the diversity of licensed vaccines.

Vaccine inequity is symptomatic of the failure of global governance of the pandemic. The haphazard way in which vaccines are currently distributed must be addressed as part of a global vaccine strategy that includes a system of intellectual-property management, manufacturing, and distribution that ensures that vaccines are made available equitably around the world. Vaccines against pandemic diseases, and the ability to manufacture them, must not be a sequestered asset that maximizes the return to pharmaceutical company executives and shareholders or increases the electability of politicians. They must be a global public good.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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Toward Simpler, Safer Treatment of Cryptococcal Meningitis

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Cryptococcal meningitis is one of the most common and serious human immunodeficiency virus (HIV)–related opportunistic infections among adults in sub-Saharan Africa, leading to an estimated 135,900 deaths every year.¹ Under the best conditions, cryptococcal meningitis is a challenge to manage and involves high-quality medical and nursing care and often prolonged hospitalization. Much of this is driven by the fact that the best outcomes are seen when the key antifungal agent, amphotericin B, is administered intravenously daily for 1 or 2 weeks.² However, treatment with amphotericin B–based regimens frequently results in substantial toxic effects, including blood dyscrasias, acute kidney injury, electrolyte disturbances, thrombophlebitis, and hepatotoxicity. Furthermore, despite the most effective treatment, short-term mortality

remains high, ranging from approximately 20% under the best available clinical trial conditions to 40 to 50% in routine care settings.³

In this issue of the *Journal*, Jarvis and colleagues⁴ report the results of a multicenter clinical trial conducted in five African countries that evaluated a simpler treatment regimen. They modified the induction phase of the all-oral regimen used in the Advancing Cryptococcal Meningitis Treatment for Africa (ACTA) trial (14 days of oral flucytosine and fluconazole),² which fell just short of being the most effective regimen in that study, by adding a single high dose of liposomal amphotericin B (10 mg per kilogram of body weight). This addition was made on the basis of phase 2 trial data from this team showing that a single high dose of liposomal amphotericin B had equivalent early fungicidal