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Perspective

## Worldwide vaccine inequality threatens to unleash the next COVID-19 variant

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## ABSTRACT

The emergence of the Omicron variant (B.1.1.529 BA.1) near Johannesburg heralded the development of an unprecedented number of new COVID-19 infections across South Africa in November 2021. Omicron and its subvariants would soon become the dominant strains across Africa, Europe, and the United States. As with the Delta variant (B.1.617.2), Omicron emerged from an industrialized nation with one of the lowest vaccination rates of any well-developed country. The emergence of variants from undervaccinated regions is a direct consequence of the virus replicating unchecked through an unprotected population. Despite this, the United States and other higher-income nations have adopted a strategy of preferentially inoculating their citizens with multiple and booster doses, whereas lower-income nations struggle with vaccine availability, infrastructure, and their own vaccine manufacturing capability. Much more needs to be done to address worldwide vaccine inequities and prevent the emergence of the next devastating variant. The persistence of the pandemic anywhere remains an ongoing threat to citizens everywhere.

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On a warm South African day in mid-November 2021, Dr. Angeliqe Coetzee examined a 29-year-old man complaining of extreme fatigue and severe headaches. The symptoms seemed more consistent with heat stroke than the sore throat and fever she had noticed in her patients with COVID-19. At the end of the day, after seeing several similar cases test positive for COVID-19, Dr. Coetzee, chair of the South African Medical Association, became convinced that something was amiss. Within a week, investigators determined that her patients were infected with a new variant possessing multiple mutations (McKeever, 2021), B.1.1.529 BA.1 or “Omicron”. Within a few short weeks, Omicron (BA.1) became the dominant strain across South Africa, Europe, and the United States and has since spawned multiple subvariants, including BA.2, BA.2.12.1, and BA.4/BA.5, with the possibility of BA.2.75 gaining ground in several countries (The Guardian, 2022).

BA.1's emergence occurred in an industrialized nation with one of the lowest vaccination rates of any well-developed country. As of July 2022, only about 33% of the South African population (Holder, 2022) was fully vaccinated versus 67% in In-

dia, 63% in Mexico, 80% in Brazil, and 67% in the United States. Africa ranks at the bottom of fully-vaccinated regions, averaging at about 19% in comparison to 69% of the worldwide population (Africa CDC, 2022). The factors leading to lower vaccination rates across the continent are complex (Adepoju, 2021). Although “vaccine nationalism” (stockpiling by higher income nations) was initially cited; other factors, such as vaccine hesitancy, fueled by rumors and disinformation, misperceptions about the protection afforded by previous exposure, supplies of syringes and other equipment, and the security of the cold chain have also received blame.

As the COVID-19 pandemic continues in its third year, the consequences of worldwide vaccine inequity in prolonging the pandemic (Oehler and Vega, 2021) are even more evident. In 2021, the World Health Organization's target for all nations to achieve at least a 10% vaccination target by September was missed by 56 countries, mostly in Africa, even as higher-income nations administered third and even fourth doses of messenger ribonucleic acid vaccines to their citizens. According to the World Health Organization, the list of countries likely to miss a 40% threshold by the end of 2022 and 70% by the mid-2023 is even larger. Impoverished countries face logistical and financial hurdles that are difficult for themselves to solve. Among them is the significant capital expenditure (estimated at between 30–60% of their existing health care budgets) necessary to vaccinate 70% of their population based

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on the current costs of available vaccines (World Health Organization, 2022).

As the BA.4 and BA.5 subvariants continue to increase the risk of reinfections and significant outbreaks in developed nations well into the second half of 2022 (Leatherby, 2022), the threat of undervaccinated nations serving as a breeding ground for the next devastating variant is easy to understand. The more a virus replicates within a specific population, the more it is likely to mutate. Although social distancing, the use of masks, and robust testing can reduce transmission in a community, widespread vaccination offers the best hope of reducing unchecked transmission and in turn, the massive burden on the health care system and the economy. In addition to reducing the severity of infections and preventing hospitalizations, COVID-19 vaccines quell transmission in one other essential fashion: by controlling viral replication. Even when breakthrough infections occur in fully-vaccinated and/or boosted individuals, they tend to be milder. Patients will often have lower viral loads, resulting in a much shorter opportunity for the virus to be transmitted to others, though this protection may wane with time. Those persons with “hybrid immunity” (immune protection in those who are vaccinated and have experienced at least one SARS-CoV-2 infection before or after vaccination) may have the same or marginally better protection than by either vaccination or natural infection alone. However, in countries with large proportions of the population unprotected by vaccination, SARS-CoV-2 strains can replicate through a population unfettered, increasing the mutation rate and establishing a breeding ground for new variants.

Although the exact reasons for the emergence of specific variants are still being elucidated, it seems clear that for the Delta (B.1.617.2) variant, low vaccination rates were also a factor in its emergence (McKeever, 2021). Once India's first COVID-19 wave peaked in September 2020, new infections subsided and were at relatively low levels the next January, when initial vaccine shipments were first targeted only to the higher risk groups (i.e., the elderly, those with comorbid conditions, and those with the highest risk of exposure). Large-scale administration of the vaccine was not planned until September 2021 because of the perception that pre-existing community exposure would inhibit a second wave. When Delta was first identified in March 2021, less than 1% of the country's 1.4 billion residents had received the jab. The resulting second surge of the new COVID-19 variant led to a staggering number of new cases and deaths across India in the spring of 2021, and Delta surged across the world for much of the remaining year.

Since late 2021, Brazil and India, origins of previous coronavirus variants, have had greater success in raising vaccination rates. By mid-2022, Brazil's fully-vaccinated percentage equaled that of the United States, and India's fully-vaccinated rate increase was trending higher than many other higher-income nations. Given the high levels of natural infection and escalating vaccination rates in these previously vulnerable nations, it seems likely that the next variant may emerge from geographic regions that combine areas of high population density and significantly low vaccination rates—placing the 1.4 billion residents of Africa, with just 21% of the population having received even a single dose (Africa CDC, 2022), squarely within the crosshairs of the next potential variant. Of the bottom 25 least fully-vaccinated countries, 21 are in Africa, leaving only Haiti, Papua New Guinea, and war-torn regions of Yemen and Syria outside of the continent (Holder, 2022).

Addressing the profound vaccine inequity that currently exists in Africa will not be easy, but experts feel that it can and must be solved. The consequences of not doing so will have profound global implications. The emergence of new variants from undervaccinated corners of the world threatens to prolong the pandemic phase and delay the onset of endemic COVID-19, a likely outcome

in which more modest ongoing levels of SARS-CoV-2 cases occur in a seasonal or low-level pattern, as in the case of the flu. A longer pandemic phase threatens to stifle economic recovery, exacerbate worldwide supply chain issues, bring hospitals and health systems to the brink of collapse, and exact a further devastating human toll. Although recent Omicron variants may cause less severe disease than Delta or other earlier variants, there is no guarantee that subsequent variants will not develop higher pathogenicity. To curtail the pandemic phase, higher-income nations must meet their commitments to share vaccine doses with international distribution partners, such as COVAX. According to the Kaiser Family Foundation, as of July 2022, of the 1.1 billion US COVID-19 vaccine doses that were pledged to global partners before 2023, only about half (564.3 million) have been delivered, with only 169 million transported to sub-Saharan Africa (Kaiser Family Foundation, 2022). Vaccine shipments need to be predictable and reliable, not *ad hoc*, a strategy that has stressed limited infrastructure in the region and has reduced inventory shelf-life. In addition to supplying vaccines, donations should include companion supplies (e.g., syringes and diluent) (World Health Organization, 2021). Higher-income nations must also help undervaccinated countries with infrastructure and cold-chain investments. Frustrated by intellectual property and technology transfer restrictions from Pharma, Afrigen, a small South African biotech company is using publicly available information and outside partners to independently replicate Moderna's messenger ribonucleic acid vaccine. Moderna has so far refused to cooperate; instead, it is intending to build its own plant within the region (Wroughten, 2022). However, two researchers at Texas Children's Hospital have developed CorbeVax (Hotez and Botazzi, 2021), a patent-free, open-source, easy-to-store, and inexpensive-to-manufacture COVID-19 vaccine, which has already been shared with Indian manufacturer, BioE, and licensed to local vaccine producers in Indonesia, Bangladesh, and Botswana. With BioE planning to manufacture a billion doses of CorbeVax in 2022, this single, privately-funded vaccine may soon be available to vaccinate more persons in developing countries than all the vaccines donated so far by the United States or any other G7 country. Lastly, it is critical to address the trust deficit that exists in undervaccinated regions, brought about by lack of knowledge on the part of providers, entrenched negative attitudes about vaccines, and social media misinformation (Nair *et al.*, 2021). Policy makers must ensure that health care workers have the resources and training to educate their patients so that the deep-seated mistrust in the health care system by many groups is addressed and that the powerful antivaccine messages on social media are countered whenever possible.

Efforts to address worldwide vaccine inequities during the pandemic have faced many challenges. Although higher-income countries prioritize booster doses, they have largely failed to recognize the urgency of immunizing the poorest and most vulnerable nations of the world, places where the next devastating variant could be destined to emerge. For as long as this continues, the persistence of the pandemic anywhere remains an ongoing threat to citizens everywhere.

### Conflicts of interest

The authors have no competing interests to declare.

### CRediT authorship contribution statement

**Richard L. Oehler:** Investigation, Writing – original draft, Writing – review & editing. **Vivian R. Vega:** Investigation, Writing – original draft, Writing – review & editing.

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