# Why the Global South is integral to the development of next-generation COVID-19 vaccines and antibody therapeutics

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**Abstract**

The threshold level of immunization coverage needed to confer population immunity for COVID-19 is not yet known, although some settings may require up to 85% of the population to be vaccinated for vaccine-induced population immunity to apply. Achieving such a goal may prompt some countries to contemplate mandating COVID-vaccination. However, attaining a threshold level of population immunity, even via vaccination mandates, is not necessarily a panacea. The emergence of variants that escape immune responses could also render a setting's previous attainment of population immunity meaningless. The extent to which immune responses protect against emerging variants is of increasing importance and speaks to the need for countries to urgently step up genomic surveillance for SARS-CoV-2 variants and openly share that data timeously. Emerging variants also underscore why COVID-19 candidate vaccines and antibody therapeutics should be trialled in diverse geographical settings. Such approaches will catalyse the development of effective next-generation COVID-19 vaccines and antibody therapeutics.

## Introduction

Since SARS-CoV-2, the causative agent of Coronavirus Disease 2019 (COVID-19), was first identified, tens of millions of people have been infected by the virus and millions have succumbed to the disease globally. As a result of an unprecedented global effort, several prototype vaccines based on the first SARS-CoV-2 sequence available, Wuhan-Hu-1, have been developed, trialled, and are being deployed globally under emergency use regulatory frameworks.[1] The discovery in South Africa of a novel lineage of SARS-CoV-2, variant B.1.351 (also known as 501.Y.V2), has been credited with prompting United Kingdom (UK) scientists to discover variant B.1.1.7,[2] which contains similar but unrelated mutations.[3] The discovery of variant B.1.351 was shared with the World Health Organisation on 4 December 2020 and has led to the discovery of other Variants of Concern (VOCs) globally. For instance, variant P.1, which first emerged in Brazil, has also been found to contain similar but unrelated mutations to those found in variant B.1.351.[4] The VOCs that emerged in South Africa, the UK, and Brazil have now spread to multiple countries.[5]

The emergence and global spread of SARS-CoV-2 VOCs highlight that counter-measures against COVID-19 will be significantly discounted unless we can quickly identify variants that could be associated with increased transmissibility, morbidity, and mortality; that evade diagnostic detection; and that impact on neutralization by convalescent sera, post-vaccination sera, and antibody therapeutics. To realise this goal, countries will have to step up genomic surveillance for SARS-CoV-2 variants and openly share that data timeously. The emergence of VOCs also underscore why COVID-19 candidate vaccines and antibody therapeutics should be trialled in diverse geographical settings. Such approaches will catalyse the development of effective next-generation COVID-19 vaccines and antibody therapeutics.

## Infection-acquired immunity may not protect against reinfection with a variant

Natural infection with a disease typically induces protective immunity against that disease. Emerging evidence, however, suggests that individuals who have already been infected with SARS-CoV-2 and who are presumed to have accumulated some level of immunity against COVID-19 may be at substantial risk of reinfection with VOCs, such as B.1.351 and P.1.[6,7] A study of blood donors in Manaus, Brazil suggests that 76% (95% CI, 67 to 98) of the population had been infected with SARS-CoV-2 by October 2020 during the country's first wave, a finding mirrored in population-based samples from other locations in the Amazon Basin.[8,9] However, a resurgence of cases in Manaus in January 2021 suggests that new SARS-CoV-2 lineages, such as P.1, may be associated with antigenic escape, resulting in many reinfections.[7] Similar concerns have emerged in South Africa, where the country's Eastern Cape province (where variant B.1.351 was first detected) was heavily affected by the country's first wave of COVID-19, which peaked in July 2020, and badly affected again when the country entered its second wave in December 2020 driven by variant B.1.351.[8,9] Thousands of suspected COVID-19 reinfections in South Africa, a rising number of COVID-19 reinfections in settings such as Israel as a result of variant B.1.351, and at least one confirmed reinfection in France with variant B.1.351 – which caused severe COVID-19 four months after the patient experienced a mild infection – suggests that variant B.1.351 has evolved the ability to

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elude previously established immune responses.[10-13] Such findings underscore the urgency to generate vaccine-induced immunity against SARS-CoV-2.

## Clinical and public health implications of mass immunization

Vaccines have been hailed as having made amongst the greatest contributions to global health of any human intervention, along with the introduction of clean water and sanitation.[14] Mass immunization – characterized as delivering immunizations to a large number of people at one or more locations in a short interval of time – has proven to be a successful strategy for preventing the spread of many infectious diseases.[15] The emergency use designation of some COVID-19 candidate vaccines has led to their mass public deployment globally. Besides providing individual protection, mass immunization programs also aim for "population immunity" – immunization of a large proportion of the population to protect the non-vaccinated, immunologically naïve, and immunocompromised individuals by reducing the percentage of vulnerable hosts to a level below the transmission threshold.[16] In addition to directly protecting a proportion of vaccinated people, vaccination programs can also indirectly reduce infection risk to all susceptible people, either by reducing the number of infected people in the population or by rendering breakthrough cases less infectious.[17] Vaccinated people who later become infected may have less viral shedding, fewer symptoms, or faster recovery time, all of which could reduce the risk of transmission to an uninfected person.[18] Early evidence emerging from countries that have successfully initiated mass COVID-19 vaccination programs suggest that some candidate vaccines demonstrate high effectiveness in real world conditions by preventing symptomatic COVID-19, hospitalization, severe illness, and death.[19]

The threshold level of immunization coverage needed to confer population immunity for COVID-19 is not yet known, although some settings may require up to 85% of the population to be vaccinated for vaccine-induced population immunity to apply.[20,21] Achieving such a goal may be prompting some countries to contemplate mandating COVID-vaccination.[22,23] However, attaining a threshold level of population immunity, even via mandatory vaccination orders, is not necessarily a panacea. Even after a threshold population immunity is attained in a setting, large outbreaks are still possible in areas where vaccination rates are low.[24] The attainment of population immunity through vaccination, however, will depend on the availability of a vaccine, its widespread uptake, and its effectiveness in the target setting. The emergence of variants that escape immune responses could also render a setting's previous attainment of vaccine-induced population immunity meaningless.

## The value of conducting genomic surveillance and clinical trials in diverse settings

Neutralizing antibodies are considered the best correlate of protection from viral infection after vaccination and as markers of immunity against reinfection after clearance of an acute infection.[25,26] Emerging SARS-Cov-2 VOCs have been found to harbour mutations that confer resistance to the neutralizing activity induced by previous infection or vaccination. Variant B.1.1.7, which emerged in the UK, is associated with increased transmissibility and a two-thirds higher case fatality than the previously circulating virus in unvaccinated populations.[27] The P.1 variant, which emerged in Brazil, is resistant to several neutralizing monoclonal antibodies and is over six times more resistant to neutralization by convalescent plasma and more than twice as resistant to sera from vaccinees than the wildtype virus.[28] In January 2021, Brazilian researchers announced that CoronaVac, a vaccine developed by Beijing-based Sinovac, was only 50.4% effective at preventing severe and mild COVID-19 in late-stage trials.[29] These findings are in sharp contrast to how CoronaVac performed in Turkey, where the vaccine demonstrated 91.25% efficacy against COVID-19. Brazilian researchers have attributed their country's disappointing trial results to the Brazilian trial's small sample size, its dosing strategy (the vaccine's 2 shots were administered 2 weeks apart, which may not have been enough time for participants to reach peak immunity), and study population (the Brazilian trial enrolled only health professionals, as opposed to the trials in Indonesia and Turkey which included the public who are deemed less at risk of infection than health workers).[29] However, it has been postulated that CoronaVac's lower efficacy in Brazil may also be due to the country's P1 variant.[30] Lower efficacy of Chinese vaccines in settings such as Brazil has prompted the head of the Chinese Centres for Disease Control to concede that China is "formally considering" options to change its vaccines to "solve the problem that the efficacy of the existing vaccines is not high."[31] Such options include adjusting the dosage, increasing the number of doses, or mixing vaccines that are made with different technologies.

The emergence of variant B.1.351, which arose in South Africa in the aftermath of the country's first wave of COVID-19, is associated with 50% increased transmissibility and immune escape.[32] The mutations in variant B.1.351 are deemed to be of particular concern as they occur within domains that are major targets of the antibody response elicited by all first generation COVID-19 vaccines being deployed globally, as well as some monoclonal antibody therapeutics. For instance, the majority of monoclonal antibodies that have been granted emergency use designation by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) appear to be futile against variant B.1.351.[33-37] Those antibodies include bamlanivimab, which appears to be completely inactive against variant B.1.351, and casirivimab, one of the two antibodies contained in an antibody cocktail (REGN-COV), which appears to be 58-fold less effective at neutralizing variant B.1.351 compared to the original virus.[38]

Multiple vaccines also appear to be considerably less effective against variant B.1.351. A pooled efficacy analysis of the AstraZeneca (ChAdOx1 nCoV-19) vaccine trials in the UK, Brazil, and South Africa yielded an overall vaccine efficacy of 66.7% (95.8% CI, 57.4 to 74.0).[39] A subsequent analysis of the efficacy of the AstraZeneca vaccine against the UK's B.1.1.7 variant demonstrated 74.6% efficacy (95% CI, 41.6 to 88.9). Alarmingly, two doses of the AstraZeneca vaccine demonstrated only 10.4% efficacy (95% CI, −76.8 to 54.8) in preventing mild to-moderate COVID-19 against the B.1.351 variant, highlighting an 86-fold reduction, including complete immune escape, in neutralizing activity against B.1.351.[40] Similarly, Johnson & Johnson announced that its COVID-19 vaccine yielded 72% preventive efficacy in the U.S compared to a modest 57% efficacy against moderate-to-severe COVID-19 in a phase 3 South African trial, a factor attributed to the B.1.351 variant.[41,42] Novavax's South African Phase 2b COVID-19 vaccine trial demonstrated a preventive efficacy of 49.4% (95% CI, 6.1 to 72.8) in the overall trial population, including HIV-positive and HIV-negative subjects, as opposed

to 89.3% preventive efficacy in the UK's Phase 3 trial.[43] Sera from Moderna and Pfizer-BioNTech vaccinees also showed substantially reduced neutralization of B.1.351 (12.4 fold lower for Moderna and 10.3 fold lower for Pfizer-BioNTech).[38]

Although immune correlates of protection against COVID-19 or infection after vaccination or natural infection are yet to be determined, real-world evidence emerging from Israel suggests an increased incidence of variant B.1.351 in vaccine breakthrough infections in individuals who have been fully vaccinated with the Pfizer vaccine.[44] Antibodies triggered by one dose of CanSinoBIO's vaccine showed a roughly four-fold drop in their ability to block the B.1.351 variant.[45] Similarly, Sputnik vaccine recipients have been found to have a median 6.1-fold reduction in neutralizing potency against the B.1.351 variant.[46] Conversely, emerging evidence indicates that antibodies elicited by B.1.351 neutralize both the early Wuhan-Hu-1 isolate and the P.1 variant, indicating high levels of cross-reactivity and suggesting that vaccines based on the B.1.351 genetic sequence may be more broadly effective.[47] Some vaccine developers, such as Moderna and Pfizer have already indicated their intention to develop new vaccine constructs based on the B.1.351 lineage.[48,49]

While these developments are welcomed, it would be unethical if next generation vaccines based on variant sequences from Global South settings were not prioritised for the countries most affected by those variants. Notwithstanding the global implications of such Global South findings, less than 5% of public SARS-CoV-2 genomes are from low and middle income countries (LMIC) despite these settings being home to 80% of the world's population.[50] The emerging data from Global South settings such as South Africa and Brazil underscore why other LMIC should develop or strengthen their viral genomic sequencing capabilities and why they should receive international support to achieve this goal. Doing so can facilitate the creation of serum escape maps, which, in turn, can inform our understanding of SARS-CoV-2 evolution.[51] Doing so will also allow developers of vaccines and antibody therapeutics to monitor genomic databases to track the evolution of new variants.

The emergence of SARS-CoV-2 variants with the ability to evade natural or vaccine-induced immunity is concerning as it suggests that new variants may continuously emerge that improve virus fitness for transmission. The conduct of COVID-19 vaccine trials in LMIC settings could highlight whether candidate vaccines are effective against locally circulating variants. Moreover, basing next generation vaccine sequences on VOCs that emerge in LMIC could yield promising vaccine candidates that elicit cross-reactive neutralizing antibodies that are effective against multiple SARS-CoV-2 variants. Similarly, monoclonal antibody therapeutics need to be trialled and made accessible and affordable to Global South settings.

## Evidentiary and regulatory implications of VOCs for next-generation vaccines

As developers develop modified vaccines based on new sequences, regulators globally should also give thought to whether modified COVID-19 vaccines already granted EUD or licensure should be authorized without the need for large-scale clinical studies. The US FDA has published guidance that pertains to COVID-19 vaccines made by the same process and manufacturer but modified to enhance efficacy against COVID-19 caused by a SARS-CoV-2 variant.[52] The guidance document stipulates the data and information needed to support the issuance of an emergency use authorisation of a modified COVID-19 vaccine. The FDA does not require large randomised control trials to test vaccines that have been modified to target variants. Instead, the recommendations call for small immunogenicity studies akin to what is required for annual modified flu vaccines. Such trials could involve a few hundred people and last a few months, instead of tens of thousands of participants over years.[53,54]

The EMA has also published a reflection paper on the regulatory requirements for modified vaccines intended to provide protection against SARS-CoV-2 variants.[55] The EMA has also noted that large-scale safety and efficacy studies are not needed for modified vaccines which have previously been granted emergency use designation, especially as doing so would present feasibility constraints.[56] Instead, the EMA has recommended that the efficacy of modified vaccines targeting variants should be demonstrated in immunogenicity studies that are designed to investigate the immune response triggered by the variant vaccine against the variant virus. According to the EMA, a small group of subjects should be randomly selected to receive either the parent or the variant vaccine. Such a 'bridging study' is intended to gather evidence to demonstrate that the immune response, measured as neutralising antibodies, triggered by the variant vaccine against the variant virus is of the same magnitude as the immune response elicited by the parent vaccine against the parent virus. The EMA also recognises that vaccination with the parent vaccine may no longer be feasible because of ethical considerations. In such instances, the EMA notes that a comparison between immune responses triggered by vaccination with the variant vaccine against the variant strain and prior data on the immune response with the parent vaccine against the parent strain could suffice for regulatory evidentiary purposes. Like the FDA, the EMA has also recommended that manufacturers study the efficacy of the variant vaccine when given as a single dose and as a booster to subjects previously vaccinated with the parent vaccine. In such enquiries, the EMA recommends that the immune response induced by one dose of the variant vaccine against the variant strain should be compared with the immune response recorded during clinical trials with the parent vaccine against the parent strain of the virus. Such strategies on the part of regulatory authorities will need to carefully balance regulatory stringency with nimbleness, as both are crucial in responding to a rapidly evolving pandemic and building public trust.

## Conclusion

Sequencing efforts to track the evolution of SARS-CoV-2 as the COVID-19 pandemic unfolds will allow for the identification and characterization of SARS-CoV-2 variants and can highlight their potential to impact COVID-19 disease transmission, disease severity, therapeutics, diagnostics, and vaccines. Such efforts will require open and timely data sharing. The conduct of COVID-19 vaccine trials in the Global South will be crucial to understanding how candidate vaccines perform against emerging variants, while basing next generation vaccine sequences and antibody therapeutics on VOCs that emerge in LMIC could realise effective vaccines and antibody therapeutics against COVID-19. Such approaches underscore why the Global South should be at the core of next-generation COVID-19 vaccines and antibody therapeutics development.

**Table 1. WHO definitions**

| **WHO definition of a Variant of Interest (VOI)** |
|---|
| A SARS-CoV-2 isolate is a Variant of Interest (VOI) if, compared to a reference isolate, its genome has mutations with established or suspected phenotypic implications, and either:<br>• has been identified to cause community transmission/multiple COVID-19 cases/clusters, or has been detected in multiple countries; OR<br>• is otherwise assessed to be a VOI by WHO in consultation with the WHO SARS-CoV-2 Virus Evolution Working Group. |
| **WHO definition of a Variants of Concern (VOC)** |
| A SARS-CoV-2 variant that meets the definition of a VOI, and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:<br>• Increase in transmissibility or detrimental change in COVID-19 epidemiology; or<br>• Increase in virulence or change in clinical disease presentation; or<br>• Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics. |

Source: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/

## WHO nomenclature for SARS-CoV-2 variants

**Table 2. WHO Variants of Concern, as of 1 June 2021**

To facilitate easy-to-pronounce and non-stigmatising labels for VOI and VOC, WHO has recommended using letters of the Greek Alphabet, i.e., Alpha, Beta, Gamma, which will be easier and more practical to discussed by non-scientific audiences.

| WHO label | Pango lineage | GISAID clade/ lineage | Nextstrain clade | Earliest document-ed samples | Date of designation |
|---|---|---|---|---|---|
| Alpha | B.1.1.7 | GRY (formerly GR/501Y.V1) | 20I/S:501Y.V1 | United Kingdom, Sep-2020 | 18-Dec 2020 |
| Beta | B.1.351 | GH/501Y.V2 | 20H/S:501Y.V2 | South Africa, May-2020 | 18-Dec 2020 |
| Gamma | P.1 | GR/501Y.V3 | 20J/S:501Y.V3 | Brazil, Nov-2020 | 11-Jan 2021 |
| Delta | B.1.617.2 | G/452R.V3 | 21A/S:478K | India, Oct-2020 | VOI: 4-Apr 2021 VOC: 11-May 2021 |

**Table 3. WHO Variants of Interest, as of 1 June 2021**

| WHO label | Pango lineage | GISAID clade/ lineage | Nextstrain clade | Earliest document-ed samples | Date of designation |
|---|---|---|---|---|---|
| Epsilon | B.1.427/ B.1.429 | GH/452R.V1 | 20C/S.452R | United States of America, Mar-2020 | 5-Mar 2021 |
| Zeta | P.2 | GR | 20B/S.484K | Brazil, Apr-2020 | 17-Mar 2021 |
| Eta | B.1.525 | G/484K.V3 | 20A/S484K | Multiple countries, Dec-2020 | 17-Mar 2021 |
| Theta | P.3 | GR | 20B/S:265C | Philippines, Jan-2021 | 24-Mar 2021 |
| Iota | B.1.526 | GH | 20C/S:484K | United States of America, Nov-2020 | 24-Mar 2021 |
| Kappa | B.1.617.1 | G/452R.V3 | 21A/S:154K | India, Oct-2020 | 4-Apr 2021 |

## Acknowledgements

This manuscript is part of an Epidemic Ethics/WHO initiative which has been supported by FCDO/Wellcome Grant 214711/Z/18/Z. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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