**Testimonial for "*COVID-19 Variants and Evolving Research Needs*"**

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## Background

Currently there are multiple SARS-CoV-2 variants circulating across the world. These variants arise through natural variation, replication errors, cross-species transmission or immune pressure. Viruses with higher viral fitness and transmissibility are more likely to become dominant in the population. While most of variants are not a cause for concern, variants that acquire mutations in the functional parts of the virus, for example the receptor binding domain (RBD) of the spike protein, raise concerns. Accelerated changes leading to multiple mutations in the infecting virus have been observed in immunocompromised patients with persistent SARS-CoV-2 infection[1,2]. In an immunosuppressed patient, who experienced persistent viral shedding over 154 days, the virus developed several genetic changes, especially in the spike gene and the RBD[1].

SARS-CoV-2 variants have been classified by the US Centers for Disease Control and Prevention (CDC) as variants of interest), variants of concern, and variants of high consequence. Until recently, there were three variants[3] that had rapidly become dominant within their countries, that were classified as variants of concern; the B.1.1.7 (VOC-202012/01), B.1.351 (501Y.V2) and P.1 (B.1.1.28.1).

The B.1.1.7 variant (23 mutations with 17 amino acid changes) was first described in the UK on 14 December 2020, the B.1.351 variant (23 mutations with 17 amino acid changes) was initially reported in South Africa on 18 December 2020 while the P.1 variant (about 35 mutations with 17 amino acid changes) was reported on 12 January 2021 from Brazil. By 5 May 2021, the B.1.1.7, B.1.351 and P.1 variants have been reported in 114, 67 and 37 countries, respectively[3]. All three variants have the N501Y mutation that changes the amino acid asparagine (N) to tyrosine (Y) at position 501 in the RBD of the spike protein. Both the B.1.351 and P.1 variants have two additional RBD mutations K417N/T and E484K. These mutations increase binding affinity of RBD to the Angiotensin-converting enzyme 2 (ACE-2) receptor ACE2[4].

In March 2021, another new variant, the CAL.20C (B.1.427 & B.1.429) variant, which was originally reported in California, was classified as the fourth variant of concern. The variant has one mutation in the RBD at position 452 (L452R) and 45% of current samples in California are this variant.

There are also several variants of interest, including: B1.525, B1.526, B.1.617 and P.2. The B.1.525 variant, which carries some of the same mutations as B.1.1.7, and the B.1.526 which carries the E484K or S477N mutation, has been spreading in New York. The B.1.617 is prevalent in India and carries the E484Q and L452R spike mutations, among its 13 other mutations. Emerging evidence from India suggests that B.1.617 spreads more rapidly and had been reported from 28 countries by May 3, 2021.

The emergence of these new variants raise four key concerns, viz. their impact on a) viral transmissibility, b) disease severity, c) reinfection rates (escape from natural immunity) and d) vaccine effectiveness (escape from vaccine-induced immunity).

***Transmissibility***

The variants of concern spread more easily and quickly than other variants, which may lead to more cases of Covid-19 in a shorter period. The B.1.351 variant has been estimated to be 50%[5] more transmissible than pre-existing variants in South Africa, and B.1.1.7 to be between 43% and 82%[6] more transmissible than pre-existing variants in the UK. The P.1 variant is estimated to be about 2.5 times more transmissible than pre-existing variants[7], while the B.1.427 and B.1.429 variants are about 20% more transmissible [8].

***Disease severity***

With regards to severity of the variants of concern, there is evidence in both directions. Hospital admission rates, clinical profile of admitted patients and hospital case fatality rates were similar in the first and second waves in South Africa. However, emerging evidence from the UK indicates that B.1.1.7 may be associated with an increased risk of death compared to pre-existing variants in the UK[9]. The variants may also indirectly increase mortality through their greater transmissibility, which rapidly overburdens health services, compromising access to, and quality of, hospital care. While there is no evidence that antivirals and anti-inflammatory treatments are affected, treatment with convalescent serum and monoclonal antibodies may no longer be effective[10-12].

***Escape form natural immunity***

With regard to escape from natural immunity, the B.1.1.7 variant showed a modest decrease in neutralization activity, by a factor of 1.5, whereas the B.1.351 variant showed complete escape from neutralizing antibodies in 48% of convalescent serum samples (21 of 44) obtained from patients who had previously had Covid-19[13]. A serendipitous finding from a vaccine trial in South Africa, in which 30% of the enrolled participants had previously been infected with SARS-CoV-2, was that the incidence of Covid-19, as confirmed on polymerase chain reaction, was 5.3% among seronegative enrollees and 5.2% among seropositive enrollees in the placebo group after 60 days of follow-up[14]. The P.1 variants also has reduced neutralization by convalescent sera[15]. For the B.1.427 and B.1.429 variants, antibody neutralization assays showed 4.0 to 6.7-fold decreases in neutralizing titres from convalescent patients [16].

***Escape from vaccine-induced immunity***

Regarding escape from vaccine-induced immunity, the B.1.1.7, B.1.427 and B.1.429 variants showed modest decreases in neutralizing activity in serum samples obtained from vaccinated persons[11,16-18]. The serum neutralizing activity for the B.1.351 variant among vaccinated persons was lower by a factor of 1.6 to 8.6 for the BBIBP-CorV vaccine[19], the BNT162b2 vaccine[17], and the mRNA-1273 vaccine[20] but was lower by a factor of up to 86, including complete immune escape, for the AZD1222 vaccine[21,22]. Neutralizing activity for the P.1 variant among vaccinated persons was lower by a factor of 6.7 for the BNT162b2 vaccine[23] and by a factor of 4.5 for the mRNA-1273 vaccine. The clinical relevance of the lower neutralization activity for either mild or severe Covid-19 is not clear. Efficacy in clinical

trials was substantially lower for two of the four vaccines tested during transmission of the B.1.351 variant in South Africa than efficacy in trials conducted in countries with pre-existing variants.

**Responses to questions from the committee**

1. *What is the state of data sharing among countries regarding variants developing and spreading across the globe?*

There are a few different databases being used to load SAR-CoV-2 sequences onto the internet. The most widely used is a database known as GISAID. Since January 2020, more than 1.5 million SARS-CoV-2 sequences have been included in GISAID. Of the 93 countries that have had more than 100,000 Covid-19 cases, 19 countries have contributed more than 1% of their viral sequences, with 5 countries (Norway, Denmark, Japan, Switzerland and the UK) contributing more than 5% of their viral sequences.

GISAID doesn't allow sequences to be reshared publicly without due acknowledgement to the original source[24]. While some researchers have regarded the GISAID processes of acknowledgement of sequence source as a hindrance, others consider it to be important acknowledgement of the scientific contributions of those who have provided the sequences. Other databases that also provide sequences on the internet such as the European Nucleotide Archive (ENA) and the NIH's *the* National Center for Biotechnology Information (NCBI) do not require acknowledgement of those who provided the original sequence. There are also websites that summarize data from these databases, such as https://outbreak.info, https://covariants.org and https://cov-spectrum.ethz.ch.

Researchers across the globe have free access to SARS-CoV-2 sequences from any of the databases providing genetic sequences on the internet. These databases are very widely used and provide a valuable repository for global information on the viruses; an essential requirement for future vaccine development.

*2. Are existing vaccines efficacious in reducing the spread of known COVID-19 variants?*

Some vaccines are highly effective against the variants of concern. For example, the efficacy of the Johnson & Johnson (J&J) vaccine was consistent across multiple variants including two variants of concern. It was 72% efficacious in the US (n=17,793; D614G variant), 68% efficacious in Brazil (n=6,666; P.2 variant) and 64% efficacious in South Africa (n=4,912; B.1.351 variant)[25]. Similarly, the Pfizer–BioNTech vaccine, which was shown to be >90% effective against pre-existing variants, has been shown in a study in South Africa to also be >90% effective against the B.1.351 variant[26]. Data from Qatar, which implemented a large-scale vaccination programme in the presence of the B.1.1.7 and B.1.351 variants shows that the Pfizer–BioNTech vaccine was 90% effective against the B.1.1.7 variant and 75% effective against the B.1.351 variant [27]. Further, the Pfizer–BioNTech vaccine effectiveness in Qatar against the B.1.1.7 and B.1.351 variants for severe, critical, or fatal disease was very high, at 97.4%[27].

On the other hand, some vaccines have reduced efficacy in the presence of variants of concern. The efficacy of the AstraZeneca vaccine 70% in the UK (D614G variant) but only 10% efficacious against the B.1.351 variant in South Africa[28,29]. Similarly, the Novavax vaccine was only half as efficacious against the B.1.351 variant as it was 89% efficacious in the UK compared to 43% in South Africa[14]. Unfortunately, the South African studies of the AstraZeneca and Novovax vaccines predominantly included young people and so had no cases of severe disease. Hence, there is no clinical evidence on whether these vaccines that have minimal, if any, efficacy for mild / moderate disease due to the B.1.351 variant of concern have any efficacy for severe disease. Some speculate, drawing upon indirect evidence, that even though some of the vaccines such as AstraZeneca are not effective in preventing asymptomatic, mild or moderate infections due to B.1.351, they may still prevent severe disease from B.1.351 infections, there is no clinical evidence for this conclusion.

*3. What role do vaccines play in reducing the spread of existing variants and the emergence of new variants?*

The vaccines play a critical role in suppressing viral replication which in turn reduces the risk of emergence of variants. However, the use of vaccines creates immune pressure on the virus, especially if there is persistent viral replication. In immunocompromised individuals there is the risk of new variants emerging[2]. If these immunocompromised individuals were vaccinated or received monoclonal antibody treatments, their persistent viral replication may lead to immune escape mutations. If such mutations enhance escape from vaccine-induced immunity, the vaccines would be rendered less effective.

The Covid-19 pandemic has illustrated that no single action is sufficient to prevent the spread of the virus. Strong public health measures against the virus must be maintained in tandem with global vaccination programs to achieve the goal of maximum suppression (see Lancet commission on Covid-19 report “SARS-CoV-2 variants: the need for urgent public health action beyond vaccines” - Annexure 1).

For viruses to succeed in spreading in a highly vaccinated population, they would need to evade vaccine-induced immunity. The current variants with predominant mutations in the receptor binding domain at positions 501, 484, 417 and 452 predate widespread availability of vaccines as most originated between October and December 2020. Over the coming months we can reasonably expect new variants to emerge that are able to escape vaccine-induced immunity because the virus is being put under pressure from widescale vaccination at present. This creates a catch-22 situation; when vaccinations are being scaled-up while viral transmission is high, as is occurring in the US and Brazil, SARS-CoV-2 has a higher likelihood of acquiring escape mutations potentially undermining the vaccine efficacy. On the other hand, one of the most effective ways to decrease transmission is to scale-up vaccination. Within this catch-22 situation, slowing viral transmission and decreasing viral replication is paramount and supersedes concerns about variants. Hence, vaccination in the presence of high transmission is strongly recommended at this time.

*4. What does the regular emergence of new COVID-19 variants tell us about the need to vaccinate the global population in order to protect the U.S.?*

Although the development of these vaccines provides hope that we can begin to control the spread of SARS-CoV-2, the inequitable distribution and availability of vaccines across the world casts doubt on how rapidly, and even if, some measure of global epidemic control will be achievable. Currently, 77% of all vaccine doses have been administered in just 10 countries (the US, China, India, the UK, Brazil, Turkey, Germany, Indonesia, France and Russia), while some countries are yet to start their SARS-CoV-2 vaccination programs. From a policy and public health perspective, global equitable access to a vaccine, particularly prioritizing protection of healthcare workers and the elderly, is the key to mitigating the worldwide public health and economic impact of the pandemic. Unfortunately, vaccine nationalism has resulted in unequal distribution of and access to SARS-CoV-2 vaccines. The Director-General of the World Health Organization (WHO), Tedros A. Ghebreyesus, has cautioned about this issue, saying “the world is on the brink of a catastrophic moral failure”.

The spread of SARS-CoV-2 in one part of the world affects all parts of the world due to extensive global connections. Even for a country with high vaccination rates, if neighboring countries have ongoing high rates of viral transmission as they have not been able to vaccinate so widely or rapidly, new outbreaks could occur and new variants could spread when the populations interact. Defeating the pandemic requires global control, which can only be achieved through the equitable global distribution of vaccines.

In addressing this problem early in the pandemic, the WHO, in collaboration with its partners, launched the Access to Covid-19 Tools (ACT)-Accelerator partnership, which supports efforts to develop tools including diagnostics, treatment, vaccines and health system strengthening to fight Covid-19. The vaccine pillar of the ACT-Accelerator initiative is known as COVAX. Initiated in April 2020 by Gavi, the Coalition for Epidemic Preparedness Innovations (CEPI) and the WHO, COVAX is a global mechanism that invests in the development, manufacturing, procurement and distribution of Covid-19 vaccine candidates, offering member countries equitable access, regardless of income level, to successful vaccines as they become available. At present, the goal of COVAX is to provide countries with enough doses to cover 20% of their populations.

The inequitable distribution of resources significantly undermines the effective management and control of the pandemic. This concern is not hypothetical or theoretical; it was demonstrated by the actions of individual states in the US in March 2020 regarding PPE and ventilators. During that period, the absence of a centralized federal government procurement strategy for these items meant that US states were competing against each other, against the federal government and even against cities to procure the necessary equipment. This resulted in prices being driven up and PPE and ventilators being distributed on the basis of available resources, rather than need, and failure to ensure equitable and effective distribution. Such maldistribution of essential Covid-19 resources leads to the loss of lives.

Exactly the same is true of vaccines. At present there is a limited number of vaccines on the market. As such, supply is fixed, and current models predict that there will only be enough vaccines to cover the world's population by 2023. Countries that can afford to pay higher prices can enter bilateral deals with pharmaceutical companies and negotiate to jump the queue. By doing so, they remove vaccines from the available pool and end up limiting vaccine allocations to other countries, which undermines the objective of systematically vaccinating the highest number of people across the globe in the shortest period of time.

According to the Duke Global Health Innovation Center, to date high-income countries have secured 4.7 billion doses, upper-middle-income countries have secured 1.5 billion doses, lower-middle-income countries have secured 731 million doses and low-income countries have secured 770 million doses. Some low- and middle-income countries (LMICs) with vaccine manufacturing capacity, such as India and Brazil, and those with the infrastructure to host clinical trials, such as Peru, have used those assets as leverage to negotiate purchase deals. However, most LMICs have not been able to secure enough vaccines.

Pharmaceutical companies, with the exception of J&J, have not adopted a single exit price for their SARS-CoV-2 vaccines. The prices are therefore open to market forces, especially as the use of non-disclosure agreements means that these companies can prevent differential pricing from become public. More demand, especially from countries under significant pressure to buy vaccines, means higher prices. High-income countries with large buying capacity are able to pay higher prices, again pushing lower income countries out of the equation and furthering inequitable distribution.

Vaccine nationalism and the hoarding of vaccines is a consequence of limited supplies. Unfortunately, SARS-CoV-2 vaccines are currently manufactured by just a handful of companies. However, there are vast capabilities throughout the world to manufacture vaccines. For example, in Africa, companies like Biovac and Aspen in South Africa, Institute Pasteur in Senegal and Vacsera in Egypt could rapidly adapt to start making SARS-CoV-2 vaccines if provided with the funding, IP rights and know-how. The reliance of LMICs on others for the development of vaccines as well as diagnostic technologies has also highlighted the dire need for these countries to increase local investments in science and technology to build self-sufficiency and enhance their capacity to control pandemics.

There is a mistaken belief by some countries that they can vaccinate their populations and then they will be safe. This simply is not true. There is no endgame that sees one country achieving sustained control of the virus while the rest of the world is dealing with rampant spread. In the Covid-19 pandemic, no-one is safe until everyone is safe. This pandemic has highlighted the inter-dependence between individuals, between communities and between countries. Each person's risk of infection is influenced as much by the actions of others as it by their own actions. The antidote to vaccine nationalism is the recognition and appreciation of our mutual inter-dependence and the need to act with all our humanity to seek a just and equitable approach to vaccine access to overcome this pandemic.

**References**


1. Choi B, Choudhary MC, Regan J, et al. Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host. N Eng J Med 2020;383:2291-3.
2. Kemp SA, Collier DA, Datir RP, et al. SARS-CoV-2 evolution during treatment of chronic infection. Nature 2021;592:277-82.
3. SARS-CoV-2 lineages - New variant report. Available from: https://cov-lineages.org/global_report.html (accessed: 11 January 2021); 2021.
4. Greaney AJ, Loes AN, Crawford KHD, et al. Comprehensive mapping of mutations to the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human serum antibodies. 2021:https://doi.org/10.1101/2020.12.31.425021

5. Pearson CAB, Russell TMR, Davies NG, et al. Estimates of severity and transmissibility of novel South Africa SARS-CoV-2 variant 501Y.V2. CMMID Repository 2021:https://cmmid.github.io/topics/covid19/sa-novel-variant.html.
6. Davies N, Barnard RC, Jarvis CI, et al. Estimated transmissibility and severity of novel SARS-CoV-2 Variant of Concern 202012/01 in England. CMMID Repository 2020:https://cmmid.github.io/topics/covid19/uk-novel-variant.html.
7. Coutinho RM, Marquitti FMD, Ferreira LS, et al. Model-based evaluation of transmissibility and reinfection for the P.1 variant of the SARS-CoV-2. medRxiv 2021:2021.03.03.21252706.
8. Deng X, Garcia-Knight MA, Khalid MM, et al. Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation. medRxiv 2021:2021.03.07.21252647.
9. Horby P, Huntley C, Davies N, et al. NERVTAG paper on COVID-19 variant of concern B.1.1.7. Available from: https://www.gov.uk/government/publications/nervtag-paper-on-covid-19-variant-of-concern-b117: SAGE meeting report; 2021.
10. Wibmer CK, Ayres F, Hermanus T, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. bioRxiv preprint 2021:doi: https://doi.org/10.1101/2021.01.18.427166.
11. Shen X, Tang H, McDanal C, et al. SARS-CoV-2 variant B.1.1.7 is susceptible to neutralizing antibodies elicited by ancestral Spike vaccines. bioRxiv : the preprint server for biology 2021:2021.01.27.428516.
12. Wang P, Casner RG, Nair MS, et al. Increased Resistance of SARS-CoV-2 Variant P.1 to Antibody Neutralization. bioRxiv : the preprint server for biology 2021:2021.03.01.433466.
13. Wibmer CK, Ayres F, Hermanus T, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nature medicine 2021.
14. Shinde V, Bhikha S, Hoosain Z, et al. Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med 2021:10.1056/NEJMoa2103055.
15. Wang P, Casner RG, Nair MS, et al. Increased resistance of SARS-CoV-2 variant P.1 to antibody neutralization. Cell Host Microbe 2021.
16. Deng X, Garcia-Knight MA, Khalid MM, et al. Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation. medRxiv 2021.
17. Wang P, Liu L, Iketani S, et al. Increased Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7 to Antibody Neutralization. bioRxiv : the preprint server for biology 2021:2021.01.25.428137.
18. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Eng J Med 2020;383:2603-15.
19. Huang B, Dai L, Wang H, et al. Neutralization of SARS-CoV-2 VARIANTS OF CONCERN 501Y.V2 by human antisera elicited by both inactivated BBIBP-CorV and recombinant dimeric RBD ZF2001 vaccines. bioRxiv preprint 2021:https://doi.org/10.1101/2021.02.01.429069.
20. Wu K, Werner AP, Moliva JI, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. bioRxiv : the preprint server for biology 2021.
21. Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Eng J Med 2021:DOI: 10.1056/NEJMoa2102214.
22. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99-111.
23. Garcia-Beltran WF, Lam EC, St. Denis K, et al. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. Cell:doi: https://doi.org/10.1016/j.cell.2021.03.013.
24. van Noorden R. Scientists call for fully open sharing of coronavirus genome data. Nature 2021;590, :195-6.

25. Sadoff J, Gray G, Vandebosch A, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Eng J Med 2021.
26. Pfizer. Pfizer and Biotech confirm high efficacy and no serious safety concerns through up to six months following second dose in updated topline analysis of landmark Covid-19 vaccine study. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-confirm-high-efficacy-and-no-serious. Accessed: 5 May 2021; 2021.
27. Abu-Raddad LJ, Chemaitelly H, Butt AA. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Eng J Med 2021:10.1056/NEJMc2104974.
28. Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med 2021:10.1056/NEJMoa2102214.
29. Voysey M, Sue Ann Costa Clemens SAC, Madhi SA, et al. Single dose administration, and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine. Lancet pre-print 2020:https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3777268.

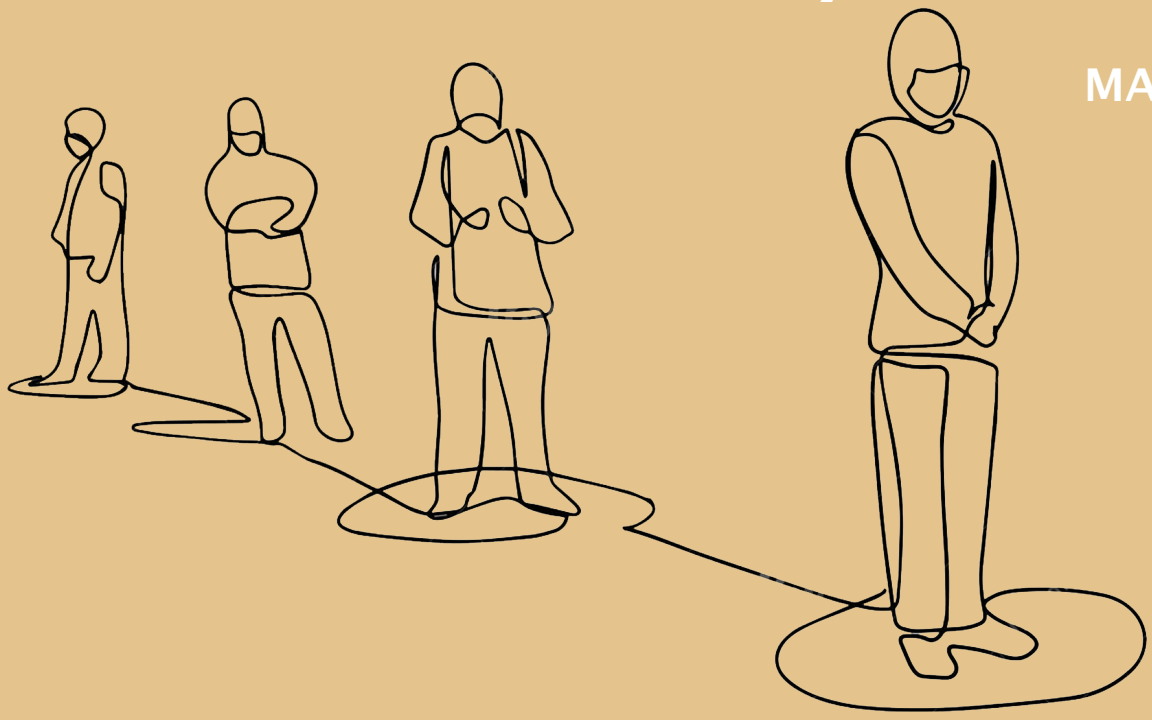
## Annexure 1:

Lancet commission on Covid-19 report “SARS-CoV-2 variants: the need for urgent public health action beyond vaccines”

THE *LANCET* COVID-19 COMMISSION
TASK FORCE ON PUBLIC HEALTH MEASURES
TO SUPPRESS THE PANDEMIC

# SARS-CoV-2 variants: the need for urgent public health action beyond vaccines

MARCH 2021




The *Lancet* COVID-19 Commission

Task Force on Public Health Measures to Suppress the Pandemic



THE *LANCET*
COVID-19 COMMISSION

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## KEY POINTS

1. SARS-CoV-2 variants of concern have emerged simultaneously in many countries, including the highly transmissible variant B.1.351, now present in at least 46 countries.

2. Lack of capacity for genomic surveillance in many countries, including some higher income countries, means that the situation may be even more serious than it appears.

3. No one is safe until everyone is safe. We are in a race against time to get global transmission rates low enough to prevent the emergence and spread of new variants overcoming immunity conferred by vaccination and prior disease.

4. Differences in the effectiveness of vaccines in providing immunity to variant B.1.351 raises the concern that current vaccines may be less effective against new and emerging variants.

5. No single action is sufficient to prevent the spread of the virus: strong public health measures against the virus must be maintained in tandem with global vaccination programs.

6. Conducting clinical trials of vaccines for every highly transmissible variant as it emerges is impracticable given the time needed to conduct them. We urgently need to identify biomarkers that can accurately predict vaccine protection against infection, disease and death.

## THE PROBLEM

At the end of 2020, there was strong hope that a global vaccination programme would render SARS-CoV-2 an endemic virus that could be contained at very low levels without further societal disruption or significant numbers of deaths. However, SARS-CoV-2 variants of concern have emerged and spread around the world, which means that current pandemic control efforts, including vaccination, are threatened.

Genetic mutations of viruses like SARS-CoV-2 emerge frequently, but some variants are labelled "variants of concern" because they have one or more of the following features:

- They can 're-infect' people who already have antibodies from a previous infection and they can infect people who have already been vaccinated, which has significant potential implications for what current vaccination programs can achieve;

- They are more easily passed from one individual to the next, which has potential implications for public health measures and for health system preparedness (given infections and hospitalizations occur more rapidly); and

- They can lead to more severe disease, which has implications for health system preparedness.

There are currently at least three documented SARS-CoV-2 variants of concern:

- B.1.351, first reported in South Africa in December 2020;

- B.1.1.7, which was first reported in the U.K. in December 2020;

- P.1, which was first reported in Brazil and Japan.

Experience in South Africa suggests that:

- Past infection with SARS-CoV-2 offers no or only very weak protection against the B.1.351 variants;

- The AstraZeneca vaccine-generated antibodies have up to an 86-fold reduction in neutralizing activity and 3.2-fold lower (70% vs 22%) clinical efficacy against mild to moderate illness for B.1.351; and

- The B.1.351 variant is about 50% more transmissible compared to pre-existing variants.

The B.1.351 variant has already been detected in at least 46 countries, including in the U.S.

If there are high levels of transmission and hence of replication of SARS-CoV-2 anywhere in the world, there will be more variants of concern, with the more infectious variants dominating. With international mobility, these variants will spread. Similar mutations are occurring in different countries simultaneously, meaning that not even border controls and high vaccination rates can protect individual countries from home-grown variants, including variants of concern, where there is substantial community transmission. Reducing community transmission is therefore paramount.

## NEED FOR URGENT ACTION

1. Maximum suppression: Public health leaders should focus on efforts that maximally suppress viral infection rates and hence preventing the emergence of mutations that can become new variants of concern (each time the virus replicates there is an opportunity for a mutation to occur), through a combination of vaccination and continued public health and behavioural measures (such as facemasks and physical distancing).

2. Global equity in vaccine access: High-income countries should support multilateral mechanisms such as COVAX vaccines and donate excess vaccine to low and middle income countries. They should strengthen laboratory research globally, enable and accelerate knowledge transfer and sharing of intellectual property. While equitable access is an important global goal, there is an overarching imperative to reduce the emergence of viral variants of concern, and this may necessitate prioritising those countries or locations with highest disease prevalence and levels of transmission, where the selective pressure and the rate of mutation are likely to be greatest.

3. Strengthen public health and behavioural interventions: in all countries to reduce the risk of further dangerous variants.

4. Capacity to accommodate surges in demand for healthcare: Health system leaders need to mobilise and support health professionals and manage increased hospitalizations over shorter periods during surges, without reducing care for non-COVID patients.

5. Preparedness: Suppression of viral infection rates and health system efforts need to be accompanied by:

    - Genomic surveillance programmes to identify and quickly characterize emerging variants in as many countries as possible around the world;

    - Rapid large-scale 'second-generation' A vaccine programmes and increased production capacity that can support equity in vaccine distribution across and within countries;

    - Studies of vaccine effectiveness in relation to existing and new variants of concern (ideally using biomarkers in laboratory studies and rapid clinical studies that yield results quickly) and living syntheses of these studies that derive implications for vaccine choice, combinations and re-vaccination;

    - Monitoring of the ability of diagnostic tests to reliably identify new variants;

    - Evaluation studies that examine need for adaptation to public health measures (e.g., double masking, duration of quarantine, approach to and frequency of testing) and to health system arrangements (e.g., hospital and long-term care visitor policies, personal protective equipment (PPE), sharing of room or ward by two or more patients who are infected with the same microorganism, Heating Ventilation and Air Conditioning systems, and surge capacity).