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

Salim S. Abdool Karim

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.

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Biography

Salim S. Abdool Karim, M.D., Ph.D., FRS

Salim S. Abdool Karim, MBChB, MMed, MS(Epi), FFPHM, DipData, PhD, DSc(hc) is a public health physician and clinical infectious diseases epidemiologist who has played a leading role in the global HIV and Covid-19 pandemic response. He is Director of the Center for the AIDS Program of Research in South Africa (CAPRISA), Durban, and CAPRISA Professor of Global Health at Columbia University, New York.

He is an Adjunct Professor of Immunology and Infectious Diseases at Harvard University, Adjunct Professor of Medicine at Cornell University, and Pro Vice-Chancellor (Research) at the University of KwaZulu-Natal, Durban, South Africa. He is an Associate Member of The Ragon Institute of Massachusetts General Hospital (MGH), Massachusetts Institute of Technology (MIT) and Harvard University. He previously served as President of the South African Medical Research Council (MRC).

He is one of the nine members of the World Health Organization's Science Council. He has been actively contributing to the mitigation of the COVID-19 epidemic in Africa, serving as a Member of the Africa Task Force for Coronavirus. He served as the Chair of the South African Ministerial Advisory Committee on COVID-19 for the first year of the epidemic. He is a Commissioner of the Lancet Commission on COVID-19.

He graduated as a medical doctor in 1983 from the University of Natal's medical school in Durban, South Africa. While at medical school he concurrently studied computer science and statistics by correspondence at the University of South Africa. He joined the Department of Virology at the University of Natal in 1986, to start his doctoral research on hepatitis B viral infection. In mid-1987, he went to New York on a Rockefeller fellowship to pursue a Masters in Epidemiology at Columbia University. During 1988, he also studied health economics at London School of Hygiene and Tropical Medicine and methods of epidemic investigations at the Centers for Disease Control (CDC) in Atlanta, USA. He completed his Fellowship in Public Health Medicine with the College of Medicine, South Africa and simultaneously graduated with a Masters in Medicine degree in Community Health from the University of Natal in 1992. He then joined the MRC and in 1993, was appointed as Director of the MRC's Centre for Epidemiological Research in South Africa (CERSA) and completed his PhD in 1999.

His main research interests are in HIV prevention, treatment of HIV-TB co-infection as well as Covid-19 prevention and treatment. His most impactful research contribution in HIV prevention was the CAPRISA 004 tenofovir gel trial, that he co-led, which provided the first evidence for the concept of antiretroviral pre-exposure prophylaxis against HIV infection. The finding has been heralded by UNAIDS and WHO in 2010 as one of the most significant scientific breakthroughs in the fight against AIDS and has been ranked among "The Top 10 Scientific Breakthroughs of 2010" by *Science*. This study also discovered that tenofovir gel prevents herpes simplex virus type 2 infection in women, the first biological prevention agent against genital herpes. He also led the team that provided the empiric evidence for the "Cycle of HIV Transmission" where young girls are most often infected by men about 10 years older. These findings provided the evidence for the UNAIDS Report "Get on the Fast-Track - The Life-Cycle approach to HIV", which has influenced the HIV response in several African countries and is listed as the highest priority in the current South African National AIDS Plan. In the field of HIV vaccines, he is co-inventor on patents which are part of HIV vaccine candidates and CAP256-VRC26.25, a highly potent broadly neutralizing antibody that is being developed for passive immunization as a prelude to future HIV vaccine development. His research on HIV-TB treatment was adopted in the WHO treatment guidelines of this co-infection and has been implemented in most countries. These significant findings have had a marked impact on HIV prevention and TB-HIV treatment in Africa and globally.

His contributions in Covid-19 have focused on the epidemiology of SARS-CoV-2 variants, including their impact on vaccine and natural immunity. His research has also assessed the impact of Covid-19 on HIV and tuberculosis.

Professor Abdool Karim's scientific contributions include over 400 peer-reviewed journal publications, including original contributions and editorials in *Science journals* (14), *Nature journals* (10), *New England Journal of Medicine* (8), and *The Lancet* (35). He is co-editor of an Epidemiology textbook (Oxford University Press), a book on HIV/AIDS in South Africa (Cambridge University Press) and a book on HIV Clinical Trials (Springer).

He is one of the world's most highly cited researchers – being listed on the Web of Science's Clarivate Analytics annual list of the world's six thousand most influential researchers by citations in the sciences and social sciences since 2018. He has 79 papers with more than 50 citations, 42 of which have been cited over 100 times – an H-index of 63. His most highly cited journal article, jointly first-authored with Quarraisha Abdool Karim (*Science* 2010; 329: 1168-1174), exceeds 1900 citations.

He is a member of the Editorial Board of the New England Journal of Medicine. He serves on the International Advisory Boards of Lancet HIV and The Lancet - Global Health. He is also a member of the Editorial Boards of Journal of AIDS, AIDS Research and Human Retroviruses, HIV and Infectious Diseases, and AIDS Reviews. He also previously served as a member of the Board of Reviewing Editors of mBio, eLife, as Associate Editor for AIDS Clinical Care and Corresponding Editor for the International Journal of Infectious Diseases. He has served as a Reviewer for more than 40 scientific journals.

He is an elected Fellow of the Royal Society. He is an elected Member of the US National Academy of Medicine. In addition, he is a Member / Fellow of the American Academy of Microbiology, Association of American Physicians (AAP), The World Academy of Sciences (TWAS), African Academy of Sciences (AAS), Academy of Science in South Africa (ASSAf) and the Royal Society of South Africa (RSSAf).

Salim S. Abdool Karim has made major contributions to global HIV policy and is actively involved in a range of initiatives that promote evidence-based science amongst policy makers as well to students and the general public. He has advised governments and international agencies in AIDS and global health such as the WHO, UNAIDS, PEPFAR and the Global Fund to fight AIDS, TB and Malaria. He served as the Chair of the UNAIDS Scientific Expert Panel and as a member of the UNAIDS-Lancet Commission on "Defeating AIDS" and co-authored the report, published in June 2015 in the Lancet, that mapped out a future direction for the global AIDS response. He is currently the Chair of the WHO Strategic and Technical Advisory Committee for HIV and Hepatitis, and a member of the WHO HIV-TB Task Force. He is a Member of the Board of the Population Council. He is a member of the Scientific Advisory Board for Global Health at the Bill and Melinda Gates Foundation.

His contributions in AIDS have been recognized nationally and internationally through several prestigious awards. He received the most prestigious scientific award in Africa - the African Union's "Kwame Nkrumah Continental Scientific Award". His other international awards include Kuwait's "Al-Sumait Prize" for research contributing to African development, the John Dirks Canada Gairdner Health Award, the "Lifetime Achievement Award" from the Institute of Human Virology, the DIA - Drug Information Association's "President's Award for Outstanding Achievement in World Health", the African Academy of Science's "Olusegun Obasanjo Prize for Scientific Discovery and Technological Innovation", Columbia University's "Allan Rosenfield Alumni Award", the "Outstanding Senior African Scientist Award" from the European Union – Developing Countries Partnership, and the "TWAS Prize in Medical Sciences" from The World Academy of Sciences (TWAS). He has also been awarded the "Distinguished Scholar Award" from the Biomedical HIV Prevention Forum of Nigeria, and the USAID "Science and Technology Pioneers Prize" (awarded to the CAPRISA 004 team) from US Agency for International

Development. In South Africa, he has received the MRC's "Platinum Medal Lifetime Achievement Award", "Gold Medal Award for Fellowship in the Art & Science of Medicine" from the South African Medical Association, the "John F. W. Herschel Medal" from the Royal Society of South Africa and the "Science for Society Gold Medal Award" from the Academy of Science in South Africa. He has been ranked as being among the 50 all-time "Legends of South African Science" by the Academy of Science of South Africa.

He has also been recognized for his broader contributions to society beyond his research through the "Hero in Medicine" Award from the International Association of Physicians for AIDS Care (IAPAC) and the "Men's Health Award" in the Science & Technology category from Men's Health magazine.

With regard to Covid-19, he was the joint recipient, with Dr Anthony Fauci, of the 2020 Sir John Maddox Prize (by Nature and Sense about Science) in recognition of his "achievements as going beyond the line of duty of government advisors on health policy, to communicate accurate medical advice to the public and policymakers during the Covid-19 pandemic – a contribution to society that surpasses even his work on HIV." Together with Dr Fauci (USA) and Dr Anders Tegnell (Sweden), he was one of the three chief government scientific advisors on Covid-19 profiled in the journal, Nature. He was invited to deliver a Keynote presentation at the Opening Special Session of the 1st International Covid-19 Conference in July 2020.

In summary, Professor Abdool Karim has had a profound impact through his HIV scientific discoveries and his leadership in both AIDS and Covid-19 in South Africa, Africa and globally.