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Viewpoint

Emerging SARS-CoV-2 Variants, Inequitable Vaccine Distribution, and Implications for COVID-19 Control in Sub-Saharan Africa

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Abstract: Since the onset of the COVID-19 pandemic, four SARS-CoV-2 variants of concern have emerged, which have shifted the clinical and epidemiological characteristics of the disease. Of concern is the impact of the emerging variants on COVID-19 vaccination programmes, with vaccination perceived as a key global pandemic control strategy. Variants of concern can reduce the effectiveness of the currently available vaccines, shift herd immunity thresholds, and promote wider vaccine inequities as richer countries hoard vaccines for booster shots for their populations without accounting for the needs of the underdeveloped countries of sub-Saharan Africa. Currently, Africa lags far behind the rest of the world, with most sub-Saharan Africa countries still to reach 50% vaccination of their eligible populations against global herd immunity thresholds of 70–90%. As long as the vaccination gap between sub-Saharan Africa and the rest of the world persists, SARS-CoV-2 will most likely persist as a significant global health threat, with continued emergence of variants of concern. Therefore, strategies to ensure wider reach of different types of vaccines on the African continent are urgently required alongside fighting vaccine hesitancy and logistical barriers to access for the marginalized populations. Sub-Saharan Africa must look for opportunities to manufacture vaccines on the continent and enhance genomic sequencing capacity as key pandemic-control strategies.

Keywords: SARS-CoV-2 variants; COVID-19; vaccine equity

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1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19) [1], a disease that has dramatically affected societies since it was declared a global pandemic in March 2020. While emerging coronaviruses have been perceived as a global health threat, the previous severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) epidemics, also caused by zoonotic coronaviruses, did not become protracted and overwhelming to the unprecedented levels seen with the COVID-19 pandemic. Globally, many countries have been affected, and the socioeconomic consequences have been devastating, with global economic recessions and loss

of sources of livelihoods [2,3]. World Health Organisation (WHO) epidemiological situation reports show that as of 7 March 2022, the cumulative number of cases of COVID-19 stood at 445, 096, 612, with nearly 6 million deaths [4]. Hence, the SARS-CoV-2 virus continues to spread inexorably, showing the inadequacy of the current public health control measures.

Relative to the rest of the world, sub-Saharan Africa was relatively spared of the direct impacts of COVID-19 in terms of morbidity and mortality from the disease at the onset of the pandemic [5]. The cumulative number of confirmed cases on the African continent as of 7 March 2022 was over 8 million, with over 11,000 incident cases in the preceding seven days, making it the least affected in absolute numbers [4]. The exact reasons for this are unknown, though postulations have included efficient public health responses (including strict lockdowns and travel restrictions), the prevailing lack of long-term care facilities for the elderly, sparse populations, immunity from exposure to previously circulating coronaviruses, hot climate, and a relatively young and dynamic population [5,6]. However, the socioeconomic effects resulting from global trade disruptions and other aspects adversely impacted by the pandemic may have had far-reaching consequences on some parts of the continent [7–9]. Subsequent epidemic resurgences have become more damaging, with increasing morbidity and mortality also witnessed in this region. As an example, in Zimbabwe, at the end of the second epidemic wave in January 2021, there were less than 35,000 confirmed cumulative cases, but during the third wave, from June to August 2021, this number rose from 38,000 to an estimated 120,000, representing a greater than 300% case increase over a three-month period, as illustrated in Figure 1 [10].

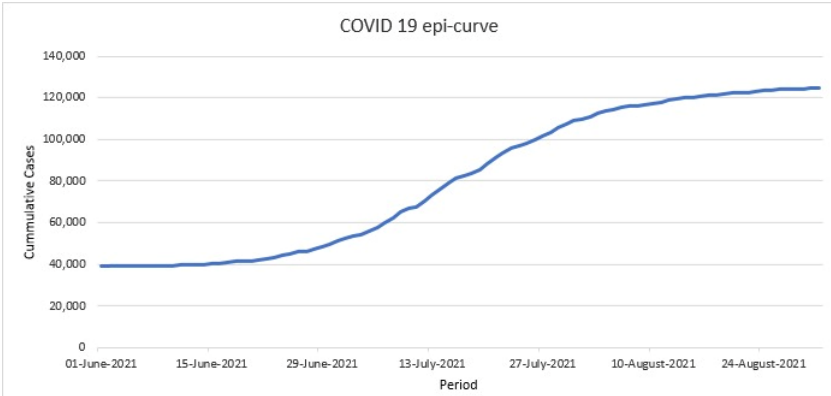

Figure 1. Zimbabwe COVID-19 epidemiological curve (June–August 2021).

In the face of uneven access and distribution of vaccines, resource-rich countries have advanced with their COVID-19 vaccination programmes, while sub-Saharan African countries significantly lag behind [11,12]. It has been argued that if these inequalities are not adequately and promptly addressed, COVID-19 might persist not only as a public health problem for Africa but subsequently for the rest of the world [13]. In this review, we discuss the emergence of SARS-CoV-2 variants of concern (VOCs) as a critical driver of the global COVID-19 pandemic, the impact of the inequitable distribution of COVID-19 vaccines on the control of the pandemic in sub-Saharan Africa, and the implications of emerging VOCs on vaccination programmes on the same continent. In our discussion, we mainly use examples from Zimbabwe as a representative sub-Saharan Africa country.

2. Drivers of the COVID-19 Pandemic

Since March 2020, when the disease was first declared a global pandemic, distinct periods of heightened transmission, known as epidemic waves, have occurred globally, with most countries having gone through at least three waves and some now in a fourth wave. International travel has been a critical factor driving the spread [14] alongside other factors, such as pandemic fatigue, lack of compliance with prevention measures, and other aspects, such as religious views related to the origins and nature of COVID-19 and falsehoods, myths, and misconceptions about the disease [15]. Of late, the realisation that SARS-CoV-2 is unlikely to be eradicated and the need to restore economies have seen governments relaxing prevention protocols and becoming reluctant to bring back stricter

prevention measures on the populace [10]. Gross human complacency and increased mobility are important drivers for continued COVID-19 transmission globally. In Zimbabwe, during the period from December 2020 to January 2021, greater than 90% of the incident cases were attributable to local transmission due to increased human mobility [16] unlike the first wave, when greater than 60% of the cases were imported from neighbouring countries [17].

SARS-CoV-2 replication is error-prone [18], as occurs with other RNA-viruses. Most of the resultant mutations have no clinical or public health significance. However, some of the mutations will give rise to variants with increased transmissibility or different clinical and epidemiological characteristics compared to predecessor variants or the ancestral wild type, giving rise to variants of interest (VOIs) and variants of concern (VOC) [19]. A SARS-CoV-2 VOI has "genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND has been identified as causing significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside an increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health" [20]. A SARS-CoV-2 VOC meets the WHO 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: increase in transmissibility or detrimental change in COVID-19 epidemiology, OR increase in virulence or change in clinical disease presentation; OR decrease in effectiveness of public health and social measures or available diagnostics, vaccines and therapeutics" [20]. The emergence of VOCs is believed to be a key driver of continued resurgences of COVID-19 globally [21]. It is essential, moving forward, to devise effective global public health policies and strategies that minimise the chances of the continued emergence of VOCs to reduce the burden of this disease on societies.

3. The Emergence of Variants of Concern

As of December 2021, four SARS-CoV-2 variants have had been classified as VOCs. The first to be characterised as such was the Beta variant, B.1.351, first detected in South Africa in September 2020. This was followed by the Gamma variant, P.1, first reported in Brazil in December 2020. Subsequently, the Delta variant, B.1.617.2, was reported for the first time in India in December 2020. More recently, the Omicron variant, B.1.1.529, was sequenced in South Africa and Botswana in November 2021. The Beta, Gamma, and Omicron variants were associated with widespread global community transmission.

The Delta variant almost displaced all variants at the time of its existence, becoming the dominant variant during the third epidemic wave. Zimbabwe's genomic sequencing results showed that the Beta variant was responsible for more than 90% of the country's COVID-19 cases in January 2021 [15,22]. Similarly, most cases in South Africa during this time were attributed to this variant [23].

African countries have limited genomic sequencing capacity. For instance, Zimbabwe has had to ship its specimens to the Quadram Institute in the UK for this critical aspect of SARS-CoV-2 surveillance [24]. Interestingly, despite some of the highest numbers of incident cases occurring in the United States of America, the United Kingdom, and Europe, new VOCs have been sequenced for the first time out of these regions. Questions have been raised regarding the transparency of some countries in reporting the detection of VOCs [25,26]. The seemingly punitive restrictions that were imposed on Southern Africa when the discovery of the Omicron variant was announced have been viewed negatively and might serve as a barrier to transparency in the future [27].

The most recently sequenced variant, Omicron, has been demonstrated to have a more extensive array of mutations compared to the previous Beta, Delta, and Gamma variants. It has higher transmissibility, and epidemiological studies are ongoing to determine the characteristics of the disease due to the variant. The daily situation reports released by the Ministry of Health and Child Care of Zimbabwe (MoHCC) demonstrate that Zimbabwe reported more than 5000 daily incident cases with over 25,000 new cases in one week for the first time since the onset of the pandemic at a time when the MoHCC confirmed that the Omicron variant had been detected in the country, too; however, others have argued that we could simply have been testing more

cases during this time than before [28]. Nevertheless, positivity rates constantly over 35% during this same period of high incident cases indicate widespread community transmission and gross under-testing; otherwise, the actual number of patients may be much higher than reported.

4. Current COVID-19 Vaccination Programs

4.1. The Global Rollout and Progress of COVID-19 Vaccination Programs

Vaccination is the best public health intervention to deal with the spread, morbidity, and mortality associated with rapidly spreading infectious diseases [29]. Historically, vaccination has resulted in eradicating smallpox from the population [29]. At the same time, polio is near eradication [30], and scientists are now looking at the prospects of eliminating cervical cancer, which is caused by human papillomavirus through global vaccination programmes [31]. In December 2020, the WHO gave emergency-use authorisation (EUA) for the first COVID-19 vaccines, marking the beginning of SARS-CoV-2 vaccination programmes. This was a historical achievement given that previous vaccines had taken decades to develop, and vaccines for HIV, which has been in existence for almost four decades, have remained elusive [32]. Interestingly, this was the first time that mRNA-based vaccines were approved for public health use, and the basket of vaccines to choose from has become much broader, with a choice of mRNA-based vaccines, adenoviral-vector-based vaccines, and inactivated virus vaccines and with several pharmaceutical players working at different paces to find solutions to the COVID-19 pandemic.

COVID-19 vaccination programmes were anticipated to save many lives and restore normalcy to people's lives and economies and enable removal of restrictions to international travel. As an unprecedented achievement, three months after approval of the first vaccines, over one billion doses of SARS-CoV-2 vaccines had been administered globally [33]. Still, not surprisingly, this was mainly in the high-income Western countries, whilst some of the low-resource countries from sub-Saharan Africa still had to initiate vaccination [13]. Despite the WHO warnings to avoid inequitable distribution of vaccines, the global programme faced several challenges, including vaccine nationalisation and hoarding without accounting for the needs of resource-limited countries. In addition, the pricing of the vaccines, including the mRNA-based Pfizer BioNTech, was beyond the reach of many sub-Saharan Africa countries, some of which were not part of the COVID-19 Vaccines Global Access Facility (COVAX), and had no access to vaccines that were included in this arrangement. Therefore, other countries, such as Zimbabwe, had to look for alternative sources of vaccines, including China, Russia, and India, whose vaccines had no WHO EUAs at that time [34].

The inequitable accessibility has resulted in differential speed towards herd immunity thresholds (HITs) globally, with the most significant gaps existing in sub-Saharan Africa, where most of the countries are still below 50% vaccination for their eligible populations, with some reportedly still at levels as low as less than 10% [13]. In contrast, the HITs for SARS-CoV-2 vaccination have been set globally at between 70–90%. Though HITs are not static with continued emergence of VOCs, the HIT provides a good target for governments to ensure wider population coverage. Additionally, the higher the vaccinated numbers of individuals, the less will be the strain exerted on public health systems during acute case resurgences in terms of severe cases requiring hospitalization and specialized treatment. Besides lack of access, the low vaccination rates in Africa have also been propagated by widespread vaccine hesitancy amidst marked mistrust, scepticism, falsehoods, rumours, myths, and misconceptions regarding these vaccines and lack of adequate efforts to address them [35–38]. Additionally, once vaccines are available, it becomes critical to address several logistical barriers to access, especially in marginalised communities with poor road and communication networks.

4.2. Vaccine Hesitancy and Unclear Vaccination Policies

The World Health Organization describes three reasons (3Cs) for not getting vaccinated —convenience, complacency, and confidence [39]. The most significant cause on the continent is that COVID-19 vaccines are inaccessible due to distribution inequalities. In cases of availability, nations also have to be content with complacency and confidence, the two driving factors for vaccine hesitancy. People could not get vaccinated because they think

they do not need it (complacency) or are concerned with vaccines' effectiveness and/or safety (confidence). Confidence is a function of how individuals acquire or receive information on vaccine efficacy [39]. Misinformation and disinformation are the main contributors of vaccine hesitancy on the continent. It is argued that addressing vaccine hesitancy is as essential as making the vaccines available to the population. As an example, just before sequencing the omicron variant, South Africa had halted fresh supplies of vaccines despite vaccinating less than 35% of the population fully at that time, as they had a massive quantity of un-administered vaccines owing to widespread denial of vaccine uptake [40]. This highlights the importance of how much the government and mainstream media need to provide precise and transparent information to dispel myths and misconception about vaccination.

Additionally, in some countries, such as Zimbabwe, there are no protocols or guidelines for vaccination of some groups, such as pregnant and breastfeeding women and school-aged children [41,42]. The lack of clear guidelines has resulted in reduced uptake of vaccines, especially among women of reproductive age, due to safety concerns [43]. If these concerns are not addressed adequately, a significant proportion of the population will remain unvaccinated, making it challenging to attain HITs.

5. Implications of Variants of Concern on the Efficacy of Current Vaccination Programmes on the African Continent

According to the WHO definition, SARS-CoV-2 VOCs have reduced susceptibility to public health interventions. Though vaccination is not the only one, it is critical, as it is the most essential strategy for pandemic control and restoring socioeconomic normalcy [44]. The Delta variant, sequenced when global vaccination programmes had commenced, largely remained susceptible to most vaccines. However, the Centre for Disease Control (CDC) showed reduced effectiveness to Pfizer BioNTech and Moderna vaccines [45]. From June–July 2021, when the circulation of the Delta variant dominated in the USA, effectiveness of these vaccines against infection dropped significantly from 74.7% to 53.1% [45]. However, these mRNA vaccines are not widely available in sub-Saharan Africa. The Delta variant remained susceptible to the Sinopharm and Sinovac vaccines commonly used in some African countries. Studies of the coronavac (Sinovac) vaccines have shown that they significantly protected against moderate and severe disease, hospitalisation, and deaths and moderately reduced incident cases [46]. A recently published test-negative case-control design to estimate vaccine effectiveness against symptomatic disease caused by the Omicron and Delta (B.1.617.2) variants in England showed that primary immunization with two doses of ChAdOx1 nCoV-19 or BNT162b2 vaccine provided limited protection against symptomatic disease caused by the Omicron variant [47]. The same study revealed that a BNT162b2 or mRNA-1273 booster after either the ChAdOx1 nCoV-19 or BNT162b2 primary course substantially increased protection but that protection waned over time [47]. Unfortunately, there has been a paucity of studies of these vaccines in sub-Saharan Africa, and results from other populations have been inferred on the African population. Moving forward, it is essential to have clear pharmacovigilance plans in place to monitor the safety and effectiveness of SARS-CoV-2 vaccines in low-resource settings [48].

However, emerging evidence has started showing reduced effectiveness of the Sinopharm and Sinovac vaccines, the Sputnik V, and the Covaxin vaccines against the Omicron variant. These are the vaccines widely used in some African settings [49,50]. Conclusive evidence of reduced effectiveness at clinical level is needed. There are also emerging concerns of reduced effectiveness of the Pfizer vaccine, which is one of the major SARS-CoV-2 vaccines globally against the Omicron variant [51,52]. Given the unusual array of mutations on this variant, this is not unexpected, and unfortunately, at the time of writing in March 2022, this VOC has now been sequenced in over 70 countries globally, implying that it is widespread. Therefore, reduced vaccine effectiveness is a crucial public health concern, requiring urgent interrogation for conclusive evidence. The debate regarding booster shots of SARS-CoV-2 vaccines has remained contentious, especially given the described disparities between low- and high-income countries that are already in existence. The need for booster shots might result in more vaccine

nationalisation and hoarding by the more affluent countries to protect their populations, whilst significant proportions of sub-Saharan African populations are still to receive their first dose.

A heterologous approach to vaccination has been proposed, where a booster dose different from the initial administered vaccines is thought to be more robust than boosting with homologous vaccines [53]. A heterologous approach will also be complex for low-resource settings with limited access to other types of vaccines unless there is a renewed strategy to make different types of vaccines available in these countries. The question of hybrid immunity where people with natural immunity are boosted with vaccines has not been adequately addressed though there is evidence to suggest superiority [54,55]. However, the duration of the naturally acquired SARS-CoV-2 immunity remains contentious and its efficacy against Omicron is unanswered for now. Otherwise, this would be an excellent option for resource-limited settings. VOCs also shift HITs for SARS-CoV-2 vaccination due to shifts in the effective reproduction numbers (Ro) [56]. More rapidly spreading VOCs require a more significant percentage of the population to be vaccinated than the ancestral wild type whose Ro was lower than the Omicron variant's. This implies a shift in vaccine acquisition timelines, which might strain further financial resources for low-resource countries as they shift their priorities.

6. The Implications of the Inequitable Distribution of Vaccines on the Emergence of Variants of Concern

The WHO has emphasized the need for equitable distribution of SARS-CoV-2 vaccines to reduce the spread of the virus and end the COVID-19 pandemic by stating that "nobody is safe until everybody is safe". Communities that are not sufficiently vaccinated will not enjoy the population wide benefits of vaccination, and as long as the SARS-CoV-2 remains in circulation, further resurgences will always be imminent. The prospects of eliminating the virus from the circulation are largely dependent on attaining global HITs. In a globalised world, VOCs spread very quickly because of increased travel. Therefore, strategies to ensure an equitable distribution of vaccines globally and optimal uptake in recipient countries are essential to propel the world towards a global HIT.

7. Enhancing Genomic Sequencing and Vaccine Production Capacity Building in Sub-Saharan Africa Remains Key

The actual origin of the VOCs remains unknown; however, South Africa has been commended for its transparency in informing the world timely of its sequencing of this VOC. Understanding the genetic epidemiology of SARS-CoV-2 is vital for informing public health control programmes, especially vaccination, and understanding the clinical and epidemiological trends of COVID-19. Globally, there are ongoing efforts to understand the genetic epidemiology of SARS-CoV-2 and its variants, such as NextStrain (https://nextstrain.org/ncov/gisaid/global, accessed on 24 December 2021). The elderly and those with comorbidities were susceptible to the ancestral wild SARS-CoV-2 variant, but subsequent variants have started affecting younger people without comorbidities, including school-going children. Therefore, genomic sequencing is an essential aspect of the surveillance of the COVID-19 pandemic. Unfortunately, most resource-limited settings have reduced capacity for this genomic sequencing and thus cannot detect VOCs in a timely manner. Countries in sub-Saharan Africa must prioritise building their genomic sequencing capacity in-country, including the laboratory equipment and human resources. One way of doing this is entering into collaborative partnerships with international research institutions and providing on the job training for local scientists. Alongside genomic sequencing capacity, the continent must build the ability to manufacture vaccines in Africa. This will reduce the costs of buying, overreliance on international developmental partners and reduce the global vaccination gap between the low- and high-resource countries. As a sign of goodwill, there must be ongoing negotiations for pharmaceutical companies to release patents to manufacture generic vaccines in sub-Saharan Africa.

8. The Need to Promote Multiple Prevention Strategies

In the face of continued emergence of VOCs, multiple prevention strategies have a significant role in controlling the spread of SARS-CoV-2. Whilst there is an urgent need to ensure equitable global availability of vaccines and ensure that all eligible populations are fully vaccinated, it is essential to continue emphasizing that despite the emergence of new VOCs,

the same prevention strategies as before still work [57]. These include appropriate wearing of facemasks, physical distancing, appropriate hand hygiene, good ventilation, and avoiding unnecessary gatherings. Now, more than ever, socially engineered pandemic controls and infection prevention and control (IPC) strategies are essential due to widespread pandemic fatigue and high human complacency coupled with increased global mobility. Omicron symptoms are generally reported as mild, which will propagate complacency, failure to observe infection prevention and control protocols, and even vaccine hesitancy.

Innovative ways of dealing with pandemic fatigue and human complacency are required. Therefore, the WHO risk communication and community engagement pillar must work with its sister pillars in various countries to develop appropriate information, education, and communication material to encourage populations, especially in sub-Saharan Africa, to adhere to prevention protocols. Africa's healthcare systems have been primarily described as fragile [58], with reduced capacity and resilience to cope with large-scale surges in cases requiring institutional treatment. Some of the African countries witnessed this during the second and third waves, with unprecedented demands for admission, oxygen, and other requirements. Additionally, a number of sub-Saharan African countries have suffered massive brain drain, especially during the COVID-19 pandemic, as skilled healthcare workers have migrated to richer countries that offer better remuneration and working conditions. Therefore, it remains essential to emphasise the need for adhering to prevention strategies in these countries.

9. Conclusions

The continued emergence of variants of concern, including the Omicron variant, demonstrated the need for new innovative approaches to tackling the pandemic. These variants have implications for COVID-19 control and vaccination programmes for sub-Saharan Africa and other under-resourced parts of the world. Failure to do so will result in the vaccines in use becoming less effective over time due to the emergence of new variants in unvaccinated individuals. There is an urgent need to address the global vaccine inequity, build genomic sequencing in low-resource countries to detect emerging variants on time, and build the capacity to manufacture SARS-CoV-2 vaccines on the African continent. This will reduce the costs of vaccines and overreliance on international developmental partners. Alongside this capacity is the need to fight vaccine hesitancy successfully, acquire safety and effectiveness data for the African population through clinical trials or pharmacovigilance, and sufficiently address the logistical barriers that can limit the uptake of available vaccines. To this end, an urgent and vital call to action to global public health stakeholders is made to address this important global health concern decisively.

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