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Leveraging on past investment in understanding the immunology of COVID-19 – the South African experience

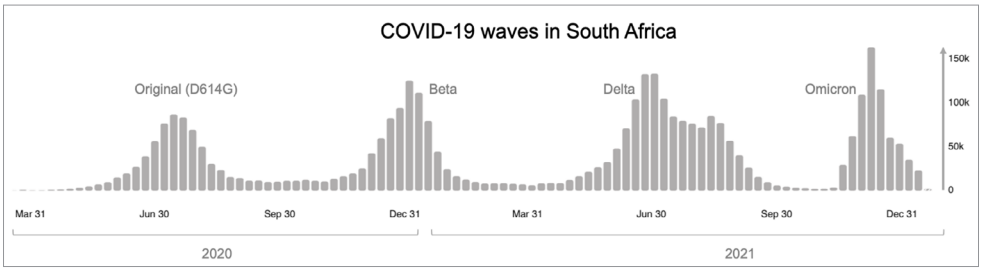
Significance:

The COVID-19 pandemic, and in particular the emergence of viral variants, resulted in an enormous global public health crisis. South African scientists, with a long history of studying viral evolution and antibody responses, were well positioned to pivot their research to focus on SARS-CoV-2. Using the expertise and infrastructure developed over decades for HIV vaccine research, South Africa took a leadership role in studying the antibody response elicited by SARS-CoV-2 infection and vaccination. We describe key scientific outcomes of those studies, and the drivers of a successful national response.

The emergence and evolution of SARS-CoV-2 in South Africa

The first confirmed case of SARS-CoV-2 in South Africa was identified on 5 March 2020; since then, the country has experienced over 3.5 million confirmed cases and over 94 000 confirmed deaths as of 25 January 2022.[1] The first wave of infections from June to August 2020 was driven by the original virus containing a D614G mutation (Figure 1). This mutation was not associated with immune escape but rather with increased transmissibility, and was the first indication that SARS-CoV-2 variants would become relevant to public health.[2] The second wave of infections in South Africa was driven by the Beta variant and lasted from December 2020 to February 2021. The Beta variant was first identified in South Africa, likely emerging from the Eastern Cape and rapidly disseminating through the country and to many other regions around the world.[3]

Despite the roll-out of the Janssen/Johnson & Johnson single-dose Ad26.COV2.S vaccine to healthcare workers from March 2021 and the rollout of the Pfizer BNT162b2 vaccine to the general adult population by August 2021, vaccination roll-out in South Africa was slow and the country experienced a deadly third wave that was dominated by the Delta variant, which was first identified in India.[4] This wave has been the longest lasting wave so far, starting in May 2021 until August 2021 and resulted in high levels of mortality and morbidity (Figure 1). The fourth wave of infections was driven by the neutralisation-resistant, highly transmissible Omicron variant which, like the Beta variant, was first described in South Africa and has now rapidly spread worldwide.[5] The Omicron variant was first identified in November 2021 and drove a fourth wave peaking relatively early in December 2021. By the end of January 2022, the fourth wave had ended, having resulted in fewer hospitalisations and deaths than prior waves (Figure 1).



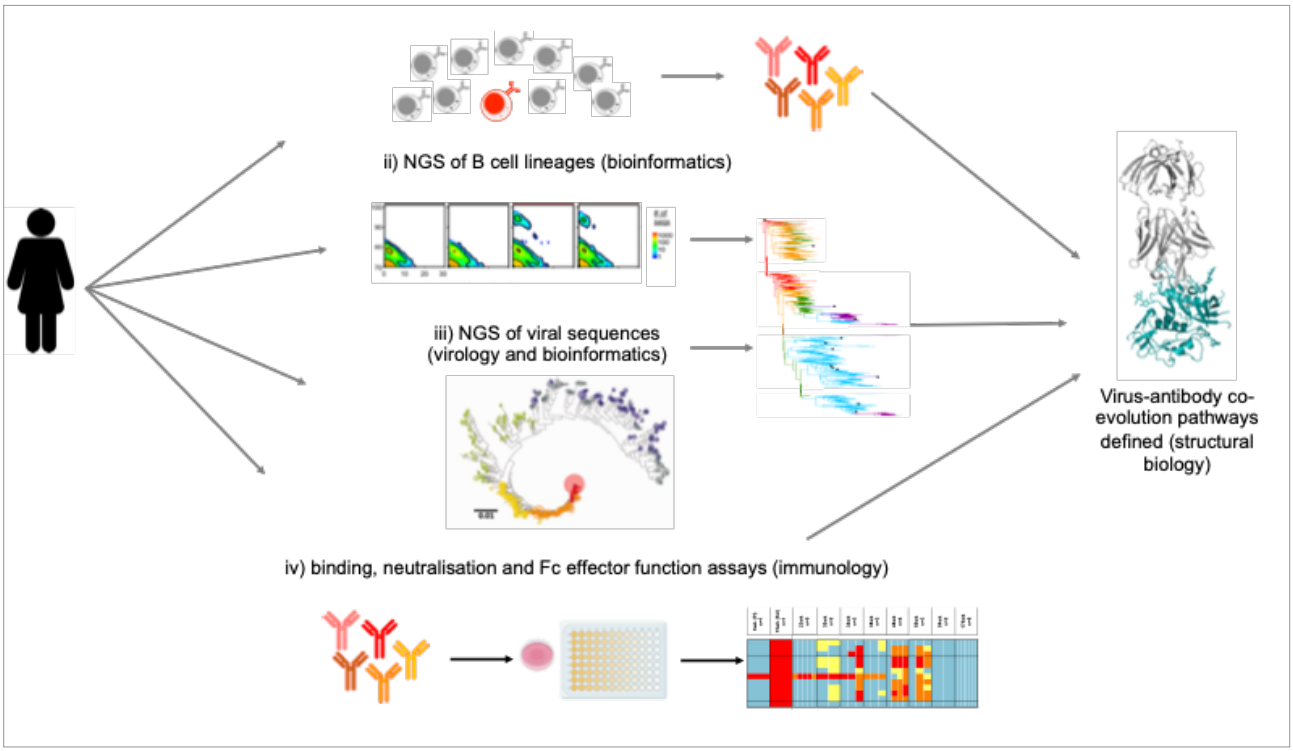
Source: Adapted from WHO COVID-19 dashboard[1]; accessed 25 January 2022

Figure 1: The four COVID-19 waves in South Africa. Since March 2020 when the first case of SARS-CoV-2 infection was identified in South Africa, the country has experienced four waves of infection which have been fuelled by different variants, resulting in high morbidity and mortality.

The COVID-19 pandemic, and in particular the emergence of viral variants in South Africa, resulted in an enormous public health crisis. As a laboratory of the National Institute for Communicable Diseases with a strong history in studying viral evolution and antibody responses, we at the Antibody Immunity Research Unit (AIRU) made the decision to pivot our research to focus on SARS-CoV-2. Over the last 2 years, we have made use of the expertise and infrastructure we have developed over more than 20 years of HIV vaccine research, to study the antibody response elicited by SARS-CoV-2 infection and vaccination. Here we reflect on how leveraging past investment in HIV vaccine research in South Africa resulted in our national ability to make major contributions to understanding the immunology of COVID-19.

The transfer of skills from HIV vaccine research to SARS-CoV-2 antibody research

For the past 20 years, the AIRU has focused on understanding the interplay between the antibody response that develops in HIV-infected individuals, and the evolution of the virus in that same person. We have extremely strong ties with the Centre for the AIDS Programme of Research in South Africa (CAPRISA), led by Prof. Salim Abdool Karim, who established a cohort of young women in 2002 and followed them for years, in many cases



NGS, next-generation sequencing
Components of the figure were generated using www.biorender.com

Figure 2: Tools used in HIV research that have been pivoted towards SARS-CoV-2 research. The Laboratory has focused on characterising the antibody response in HIV-infected individuals as well as tracking the evolution of the virus over time. We have used our combined skills across multiple platforms to answer key questions in the HIV field and have adapted these technologies to study antibody responses to SARS-CoV-2.

after they became HIV infected. From this cohort we have access to invaluable plasma and cell samples from acute infection through to chronic infection. This allowed us to track how the antibody response develops over time and changes as the virus mutates, both impacting the evolution of one another.[6-8] These virus–antibody co-evolution studies have enabled us to understand how special antibodies, known as broadly neutralising antibodies (bNAbs), develop and mature over time. These bNAbs are widely assumed to be essential for a future HIV vaccine because they are able to recognise and neutralise diverse, global HIV strains, despite the ever-evolving nature of the virus. Therefore, producing such a response upon vaccination would be desirable for HIV prevention. However, in HIV infection, these broadly neutralising antibodies are rare, and only develop after many years in a subset of individuals (less than 20%). Therefore, understanding the best path to quickly produce these antibodies is a key question in the HIV vaccine field. We use various tools across a wide range of biological sciences to answer these questions. These platforms include virology, immunology, structural biology, and bioinformatics, with senior members of the team leading niche areas in a highly collaborative, multidisciplinary model of research (Figure 2).

Transitioning from HIV to SARS-CoV-2 antibody research

Strong, long-lasting collaborations have been a key factor to the success of the AIRU, enabling the team to rapidly learn and adopt state-of-the-art technologies. Over the years, we have established lasting collaborations throughout the globe (Figure 3). Many of the collaborators who we have worked with over the past 20 years have also re-focused to study SARS-CoV-2 and we have continued working together. The pandemic has also resulted in the development of new collaborations, mostly in South Africa (Figure 3). Prior to the pandemic, the AIRU had a strong focus on building collaborations with other basic scientists; however, during the last 2 years, the Unit has become increasingly connected with clinicians and epidemiologists, enabling us to have a strong translational focus. This connection has strengthened our research, and that of our collaborators, enabling individuals with different perspectives to tackle a common question in a more innovative manner. In addition, laboratories around the world have rapidly shared reagents, consumables which are in short supply, as well as their data, enabling the field to move extraordinarily fast. The use of preprint servers to disseminate data rapidly has increased as researchers aim to share their latest findings prior to formal peer review. While lack of peer review comes with obvious disadvantages, these are offset by increased transparency and timely sharing of results.

Throughout the pandemic, it was not only staff members in the Laboratory who contributed to SARS-CoV-2 research, but also the master's and PhD students whom we mentor. During the 'hard lockdown' which occurred in the first wave, many students were unable to access the Laboratory, which led to uncertainty about whether their degree programmes would be delayed. Nonetheless, when they returned to the Laboratory when restrictions were eased and non-essential work could resume, most students volunteered to help with the SARS-CoV-2 components of the research while they caught up on their own individual research projects.

Funding bodies have also been critical in facilitating the research we conduct, both pre- and post-COVID-19 pandemic. We have historically received much of our laboratory funding from grants provided through the US National Institutes of Health (NIH), the International AIDS Vaccine Initiative (IAVI)), and the United States Agency for International Development (USAID). Fogarty grants from the NIH provided essential medium-term training for students and staff to be hosted in international laboratories. This international funding was essential in developing our expertise and platforms for HIV research. However, since the COVID-19 pandemic hit, we have been strongly supported by local government funding agencies through the South African Medical Research Council and the South African Department of Science and Innovation. Local government support has been key to the success of the country's research and development and enabled South African researchers to be internationally recognised leaders in SARS-CoV-2 research. Although

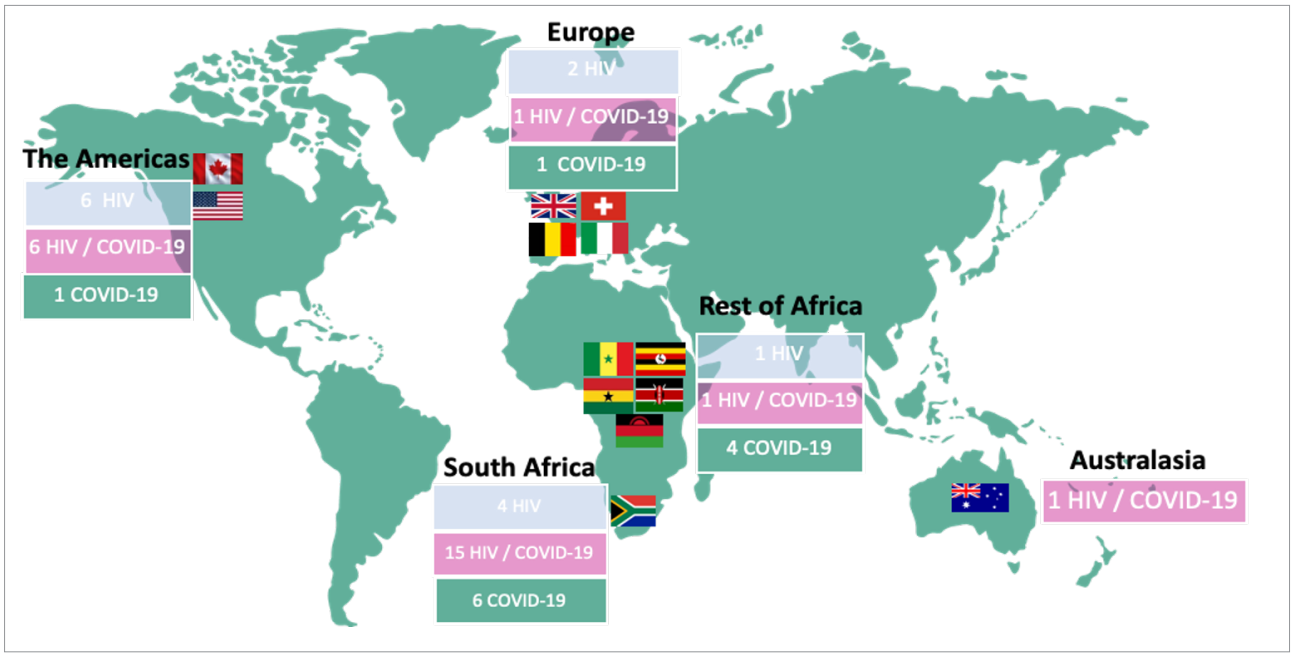


Figure 3: Map of global collaborations. One of the reasons for the success of the Laboratory is our collaborations which span across the globe and across disciplines. We have established HIV-related collaborations (blue), COVID-19-related collaborations (green) and collaborations which span both HIV and SARS-CoV-2 viruses (pink). The number of collaborators in each region is shown as a number in each box. The location of the collaborators is shown by a flag on the continent.

this emergency short-term funding has been crucial and timely, sustainable funding will be essential to ensure that research efforts are not jeopardised once the pandemic stabilises.

Key findings from our SARS-CoV-2 research over the past 2 years

The AIRU has been very involved in research on the virology, bioinformatics and structural biology of SARS-CoV-2, all of which was enabled by our previous studies on HIV. Upon the emergence of the Beta variant, our experience and knowledge of structural biology from HIV studies enabled our Unit to identify the key mutations within the receptor-binding domain and the N-terminal domain that would likely confer neutralisation resistance. Having identified them, we introduced these mutations into the spike protein of the original virus and tested them for binding and neutralisation. The data showed that the Beta variant was extremely neutralisation resistant compared to the original virus.[9] Beta was the first SARS-CoV-2 variant to contain major immune escape mutations that affect neutralisation by key antibody classes that target the SARS-CoV-2 spike protein.[9] These data led to a follow-up study looking at the response elicited by Beta variant infection. Interestingly, we found that individuals infected with the Beta variant had more cross-reactive antibodies, with a minimal drop in potency against the original virus and no drop in potency against the Gamma variant.[10] This suggested the possibility that Beta could form the basis of an improved second-generation vaccine.

We also characterised the antibody response to the Delta variant in South Africa and continued to be very involved in the virology and bioinformatics aspects of the pandemic with the discovery of the C.1.2 lineage, again using our experience of studying HIV envelope evolution, which is also driven in large part by antibody pressure.[11] The C.1.2 variant contained approximately 34 mutations in the spike protein and our immunological analysis showed neutralisation resistance of this variant towards plasma from vaccination and prior infection.[11] We continue to use our bioinformatics expertise to contribute to surveillance efforts across the country for detection of emerging variants. As our Laboratory is part of the Next-Generation Sequencing South Africa (NGS-SA) Consortium, we were at the forefront, together with our collaborators, in identifying the novel Omicron variant.[5] Similarly, as for Beta and C.1.2, our structural biology knowledge allowed us to postulate that the RBD and NTD mutations in the Omicron variant would likely render this variant highly neutralisation resistant. We also contributed to a study showing neutralisation resistance of Omicron in individuals.[12] Our next-generation sequencing expertise, honed over many years of HIV work, continues to be utilised in the high-throughput sequencing of not only viral genes but antibody genes from individuals with prior COVID-19 disease and/or after vaccination.

Early in the pandemic, we rapidly developed and implemented serological binding and neutralisation assays that enabled us to measure antibodies from individuals who had been infected with SARS-CoV-2. This work was enabled by previous HIV collaborations which accelerated development of assays, and enabled swapping of samples and concordance assays which gave us confidence that our new assays were comparable with data being generated internationally. In this role, we contributed to a convalescent plasma trial aimed at treating SARS-CoV-2 infected individuals with antibodies from recovered patients. This was work conducted in collaboration with the South African National Blood Service.[13] We have also been part of sero-survey studies, not only in South Africa but in other African countries too.[14]

In addition to understanding the immune response in individuals infected with the virus, we also embarked on large collaborations to understand the antibody response elicited by COVID-19 vaccines in the South African population. We have been part of serology studies looking at the ChAdOx1 nCoV-19 (AZD1222) vaccine in the South African context during the first and second waves of infection[15] and characterised the response to the same vaccine in South African HIV-infected individuals[16]. Our data showed that HIV-infected individuals developed strong antibody responses after vaccination. However, the Beta variant was able to escape plasma neutralisation responses elicited by the ChAdOx1 vaccine which raised concern about the efficacy of the vaccine during the Beta wave. The clinical data indicated that the ChAdOx1 vaccine had reduced efficacy against the Beta variant, although the trial was small, and on the basis of these data, roll-out of this vaccine was halted, and other vaccines were deployed. Although this decision has since been questioned based on what we now know about humoral and T cell immunity, this is the best example of how our basic research helped inform policy in real time in South Africa.

As the single-dose Ad26.COV2.S vaccine developed by Johnson & Johnson is one of the two approved vaccines in the country, we have also been extensively involved in characterising the antibody response elicited by this vaccine. During the Beta wave, we tested plasma from individuals vaccinated with the Ad26.COV2.S vaccine and found significant drops in neutralisation against the Beta variant despite high binding cross-reactivity.[17] In collaboration with a research team led by Prof. Wendy Burgers and Prof. Ntobeko Ntusi from the University of Cape Town who looked at the T cell response, we assessed binding, neutralisation and Fc effector function assays in individuals with no prior infection or who were previously infected, followed by Ad26.COV2.S vaccination. We found that individuals with prior infection mounted significantly higher levels of immune responses upon vaccination compared to previously uninfected individuals.[18] The inverse is also true; individuals who were vaccinated with the Ad26.COV2.S vaccine and then had a breakthrough SARS-CoV-2 infection had potent antibody responses which were cross-reactive against a variety of variants of concern, including Omicron, as well as SARS-CoV-1.[19]

The immunology research we undertake also spans flow cytometry and cell sorting techniques which were implemented to study the immune response to HIV infection, and to enable isolation of potent neutralising antibodies. We have successfully isolated monoclonal antibodies from individuals who recovered from SARS-CoV-2 infection, including an antibody that recognises a shared epitope on Beta and Omicron.[20] We are currently implementing high-throughput antibody isolation techniques which will allow us to isolate numerous, diverse monoclonal antibodies at a rapid pace, and which will also feed back into accelerating our HIV work. Our antibody isolation work forms part of a larger network of laboratories that have received support from the Bill and Melinda Gates Foundation. The Global Immunology and Immune Sequencing for Epidemic Response (GIISER) programme aims to facilitate the rapid isolation and characterisation of novel SARS-CoV-2 antibodies and use them for various applications such as therapeutics, diagnostics and immunogen design. The goal of the programme is to build expertise across the developing world, not only for use in SARS-CoV-2 research but also for other current and future pathogens.

Summary

Over the last 20 years, the AIRU has focused on understanding the development of broadly neutralising antibodies which target HIV. Since the start of the COVID-19 pandemic, we have pivoted our research to include studying the SARS-CoV-2 antibody response. The quick transition was facilitated by the already established expertise and infrastructure that was developed over two decades for HIV work. Without prior funding, support from government agencies and international grants, our Laboratory and many other South African laboratories would not have been able to perform this important research in such an effective manner. This past investment enabled the country to track the evolution of variants of concern, to define their phenotypic characteristics, and to evaluate immune responses to vaccination and infection in South Africa. The response to the SARS-CoV-2 pandemic has highlighted the fact that science can progress faster if laboratories around the world participate in collaborative science. This includes greater resource sharing as well as the development and preservation of existing tools to allow for open data sharing. The sustainable availability of funding is crucial in the development of strong centres of research excellence, and, therefore, increased funding from local and international funding agencies, across various fields, would aid in the advancement of science globally. Lessons learnt from the COVID-19 pandemic should be used to advance research to combat diseases which have been with us longer than SARS-CoV-2, such as HIV/AIDS, as well as to plan for future pandemics.

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Competing interests

We have no competing interests to declare.

References

1. World Health Organization (WHO). WHO Coronavirus disease (COVID-19) dashboard [database on the Internet]. Geneva: WHO; 2020 [cited 2022 Jan 25]. Available from: https://covid19.who.int/region/afro/country/za
2. Zhou B, Thao TTN, Hoffmann D, Taddeo A, Ebert N, Labroussaa F, et al. SARS-CoV-2 spike D614G change enhances replication and transmission. Nature. 2021;592(7852):122–127. http://dx.doi.org/10.1038/s41586-021-03361-1
3. Tegally H, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J, et al. Detection of a SARS-CoV-2 variant of concern in South Africa. Nature. 2021;592(7854):438–443. http://dx.doi.org/10.1038/s41586-021-03402-9
4. Tegally H, Wilkinson E, Althaus CL, Giovanetti M, San JE, Giandhari J, et al. Rapid replacement of the Beta variant by the Delta variant in South Africa [preprint]. medRxiv. 2021:2021.09.23.21264018. http://dx.doi.org/10.1101/2021.09.23.21264018
5. Viana R, Moyo S, Amoako DG, Tegally H, Scheepers C, Althaus CL, et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa [preprint]. medRxiv. 2021:2021.12.19.21268028. http://dx.doi.org/10.1101/2021.12.19.21268028
6. Bhiman JN, Anthony C, Doria-Rose NA, Karimanzira O, Schramm CA, Khoza T, et al. Viral variants that initiate and drive maturation of V1V2-directed HIV-1 broadly neutralizing antibodies. Nat Med. 2015;21(11):1332–1336. http://dx.doi.org/10.1038/nm.3963
7. Wibmer CK, Bhiman JN, Gray ES, Tumba N, Abdool Karim SS, Williamson C, et al. Viral escape from HIV-1 neutralizing antibodies drives increased plasma neutralization breadth through sequential recognition of multiple epitopes and immunotypes. PLoS Pathog. 2013;9(10), e1003738. http://dx.doi.org/10.1371/journal.ppat.1003738
8. Doria-Rose NA, Schramm CA, Gorman J, Moore PL, Bhiman JN, Dekosky BJ, et al. Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies. Nature. 2014;509(7498):55–62. http://dx.doi.org/10.1038/nature13036
9. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, et al. SARS-CoV-2 501Y. V2 escapes neutralization by South African COVID-19 donor plasma. Nature Med. 2021;27(4):622–625. http://dx.doi.org/10.1038/s41591-021-01285-x
10. Moyo-Gwete T, Madzivhandila M, Makhado Z, Ayres F, Mhlanga D, Oosthuysen B, et al. Cross-reactive neutralizing antibody responses elicited by SARS-CoV-2 501Y.V2 (B.1.351). N Engl J Med. 2021(384):2161–2163. http://dx.doi.org/10.1056/NEJMc2104192
11. Scheepers C, Everatt J, Amoako DG, Tegally H, Wibmer CK, Mnguni A, et al. Emergence and phenotypic characterization of C.1.2, a globally detected lineage that rapidly accumulated mutations of concern [preprint]. medRxiv. 2021:2021.08.20.21262342. http://dx.doi.org/10.1101/2021.08.20.21262342
12. Cele S, Jackson L, Khan K, Khoury D, Moyo-Gwete T, Tegally H, et al. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. Nature. 2022;602:654–656. http://dx.doi.org/10.1038/d41586-021-03824-5
13. Glatt TN, Hilton C, Nyoni C, Swarts A, Swanevelder R, Cowley J, et al. Rapid and successful implementation of a COVID-19 convalescent plasma programme – The South African experience. Viruses. 2021;13(10):2050. http://dx.doi.org/10.3390/v13102050
14. Mandolo J, Msefula J, Henrion MYR, Brown C, Moyo B, Samon A, et al. SARS-CoV-2 exposure in Malawian blood donors: An analysis of seroprevalence and variant dynamics between January 2020 and July 2021. BMC Med. 2021;19(1):303. http://dx.doi.org/10.1186/s12916-021-02187-y
15. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384(20):1885–1898. http://dx.doi.org/10.1056/NEJMoa2102214

16. Madhi SA, Koen AL, Izu A, Fairlie L, Cutland CL, Baillie V, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 in people living with and without HIV in South Africa: An interim analysis of a randomised, double-blind, placebo-controlled, phase 1B/2A trial. Lancet HIV. 2021;8(9):e568–e580. http://dx.doi.org/10.1016/S2352-3018(21)00157-0

17. Moore PL, Moyo-Gwete T, Hermanus T, Kgagudi P, Ayres F, Makhado Z, et al. Neutralizing antibodies elicited by the Ad26.COV2.S COVID-19 vaccine show reduced activity against 501Y.V2 (B.1.351), despite protection against severe disease by this variant [preprint]. bioRxiv. 2021:2021.06.09.447722. http://dx.doi.org/10.1101/2021.06.09.447722

18. Keeton R, Richardson SI, Moyo-Gwete T, Hermanus T, Tincho MB, Benede N, et al. Prior infection with SARS-CoV-2 boosts and broadens Ad26.COV2.S immunogenicity in a variant dependent manner [preprint]. medRxiv. 2021:2021.07.24.21261037. http://dx.doi.org/10.1101/2021.07.24.21261037

19. Kitchin D, Richardson SI, Van der Mescht MA, Motlou T, Mzindle N, Moyo-Gwete T, et al. Ad26. COV2. S breakthrough infections induce high titers of antibodies capable of neutralizing variants of concern [preprint]. medRxiv. 2021.11.08.21266049. http://dx.doi.org/10.1101/2021.11.08.21266049

20. Moyo-Gwete T, Madzivhandila M, Mkhize N, Kgagudi P, Ayres F, Lambson B, et al. Shared N417-dependent epitope on the SARS-CoV-2 Omicron, Beta and Delta-plus variants [preprint]. medRxiv. 2022. https://doi.org/10.1101/2022.04.24.22273395