South Africa should be using all the COVID-19 vaccines available to it – urgently

The health and economic effects of SARS-CoV-2 have been devastating to South Africa (SA). At the time of writing, the country is ill-prepared for mitigating a third wave, with only a minority of largely urban health workers being vaccinated against COVID-19 and roll-out to the general population yet to start. This despite SA being the first country on the continent to receive vaccines – 1 million AstraZeneca SARS-CoV-2 (AZ) vaccine doses on 1 February 2021.

We note with dismay the reselling of the AZ vaccines to the African Union[1] despite the B.1.351 variant, the dominant variant during SA's second wave, circulating in much of Africa. We believe that SA has squandered the opportunity to protect at least half a million of its most vulnerable citizens before the next resurgence, with massive healthcare and economic cost. Alternatives to the AZ vaccine will not be available to South Africans within the next few months to make up the shortfall.

Why has there been a refusal in the National Department of Health (NDoH) and the Ministerial Advisory Committee on Vaccines (MAC-Vac) to use the AZ vaccine locally? The continued insistence by the NDoH and the MAC-Vac on not using it is out of step with recommendations by the World Health Organization (WHO) and other normative agencies, and the current state of vaccine science.[2,3] Unfortunately, none of the MAC-Vac's advisories, rationales or decisions have been published in the public domain since 3 January 2021, and none of the debate around specific vaccine choices has therefore been open to the public or the broader scientific community. From media interviews, the chief reason appears to be concern about the lower efficacy against the B.1.351 variant. This followed findings from a study conducted in SA that failed to demonstrate efficacy of >60% (the hypothesis being tested and for which the study was powered to address) against infection with COVID-19, after two vaccine doses.[4] The study demonstrated a 75% reduced risk of mild to moderate COVID-19 caused by the first-wave ancestry virus 14 days after the first dose, but with no significant protection against mild to moderate disease caused by the B.1.351 variant after two doses of the vaccine. There were no severe COVID-19 cases in either the vaccine or the placebo arm, as the participants were young and largely healthy; this study was not suited to assess whether the AZ vaccine protects against severe disease, which is largely seen in older patients and those with serious comorbidities, whether caused by B.1.351 or any other variant. Animal challenge studies following AZ vaccination have reported 9-fold reduction in neutralising antibody activity against the B.1.351 variant relative to ancestry virus, similar to that observed for natural induced antibody following infection by prototype-like virus infection.[5] However, immunised animals were fully protected against severe lower respiratory tract infection following challenge by the variants.[6]

SA's muddled procurement strategy is further demonstrated by the commitment to buy 20 million doses of the Pfizer vaccine, for which there is no clinical evidence of efficacy against the B.1.351 variant. We agree with the decision to purchase the Pfizer vaccine, but the NDoH must concede that it then makes a mockery of the argument that we cannot use the AZ vaccine because of a lack of data against severe disease caused by this same B.1.351 variant. The Pfizer vaccine, like most other first-generation COVID-19 vaccines, is likely to confer high levels of protection against severe COVID-19, even caused by the B.1.351 variant. Nevertheless, laboratory testing has demonstrated 3-fold or more reduction of the vaccine-induced neutralising antibody against the B.1.1351 variant relative to activity against the ancestry virus, suggesting that there would be diminished protection against mild COVID-19 caused by the B.1.1351 variant. Intriguingly, SA has not included the Novavax vaccine as part of its roll-out strategy, despite this being the only COVID-19 vaccine to report on efficacy (49 - 60%) against mild to moderate COVID-19 caused by the B.1.351 variant, and 100% protection against severe COVID-19.[7] The only other COVID-19 vaccine that SA has now committed to purchasing is the Johnson & Johnson (J&J) vaccine, for which efficacy against severe COVID-19 caused by the B.1.1351 variant is 82%, while efficacy against mild illness caused by the B.1.351 variant is yet to be reported on. The Moderna, Sputnik V and Sinopharm vaccines, with no public commitment to procure by the NDoH, have similarly not had B.1.351 data reported.

To summarise the evidence, the AZ vaccine is extremely safe and provides near-total protection against severe COVID-19 caused by ancestry virus, much like other vaccines such as the J&J, Pfizer, Moderna, Novavax and Sputnik-V.[8,9] There are no published data on the Sinopharm vaccine, which is also widely used. Prior natural infection with SARS-CoV-2 is similarly highly protective against severe COVID-19,[10,11] while it may not protect against mild infection by the B.1.351 variant[7] (Fig. 1 and Table 1). Taken together, the data suggest that COVID-19 vaccines (or prior infection) may not provide sterilising immunity or protect against mild COVID-19 caused by the B.1.351 variant, because of the relative resistance of this variant to antibody-neutralising activity. Nevertheless, the current first-generation spike-protein-based COVID-19 vaccines are likely to still confer substantial protection against severe disease,[13] because vaccine-induced CD8 (natural killer) cell responses are largely unaffected by mutations observed in the B.1.351 spike protein. It will be impossible to fully assess the impact of each COVID-19 vaccine against the B.1.351 variant and other similar variants that continue evolving, so we are reliant on a combination of immunogenicity studies, clinical trials, animal model challenge studies and observational data from mass vaccination programmes.[14] All data points suggest that the current first-generation COVID-19 vaccines induce sufficient immunity to substantially reduce the risk of severe COVID-19, and no data suggest the contrary. Misguided comparisons of different endpoints from different studies, evaluated in different population demographics, done in different countries and at different times, have been used as evidence that the AZ vaccine may be inferior to other vaccines. Although the AZ vaccine does not reduce the risk of mild COVID-19 caused by the B.1.351 variant, even if the protection against severe disease and death afforded by the AZ vaccine ends up being just half or a third of what it is with comparator vaccines (a highly unlikely scenario), it is irresponsible to pass up the opportunity to reduce the number of deaths in the absence of alternative vaccines.

Where the AZ vaccine is in use, mortality in vaccinated populations has plummeted, including in the UK, home to its own more infectious and virulent B.1.1.7 variant.[15] The fact that 'breakthrough' infections by variants, causing hospitalisation and death, have not been reported in tens of millions of Europeans given the AZ vaccine, is highly reassuring.

Cost or a desire 'not to waste money' has been cited as a reason for delaying use and reselling of the AZ vaccine, an argument comprehensively disputed when matched against the cost of infection

Company	Platform	Doses	Non-clinical results	# with vaccine (same placebo)	Protection from COVID-19 hospitalization	Protection from COVID severe dz (some at home)	Efficacy against milder COVID
moderna	mRNA-1273 mRNA in lipid nanoparticle	2	Neutralizing Abs; Strong Th1 CD4+ protection from challenge (macaques)	~15,000	97% (1 in vaccine arm after 2nd dose hospitalized)	97% (30 cases in placebo arm; 0 in vaccine reported but 1 severe per FDA)	94.1%
Pfizer	BNT162b2 mRNA in lipid nanoparticle	2	Neutralizing Abs; Strong Th1 CD4+, CD8+; protection from challenge (macaques)	~18,600	100%	100% (9 cases in placebo arm; 0 in vaccine- 1 initially severe but not)	95%
Johnson&Johnson	JNJ-78436725 Non-replicating human adenovirus/DNA	1	Neutralizing Abs; Strong Th1 CD4+ > Th2; CD8+; challenge protection (macaque)	~22,000 US, Latin America, S. Africa	100%	85.4% across 3 sites (7 deaths, 16 hospitalizations, all in placebo arm)	72% US; 61% Latin America; 64% S. Africa (95% B1.351)
AstraZeneca	AZD 1222 Non-replicating Chimp Adenovirus-DNA	2	Neutralizing Abs; Strong Th1 CD4+ > Th2; CD8+; protection from challenge (macaques)	~24813 (UK, SA, US/Peru/ Chili)	100%	100% (UK, 15 placebo arm hospitalized, 0 in vaccine; US, 5 severe in placebo, 0 vaccine)	79% overall US; 70% UK; S. Africa trial halted for mild
NOVAVAX	NVX-CoV2373 Spike protein/RBD + Matrix M adjuvant	2	Neutralizing Abs; Strong Th1 CD4 > Th2; challenge protection (macaques)	~8833 (Phase 3 UK; 2b SA)	100%	100% (10 severe in placebo in UK/SA; 0 in vaccine)	96.4% UK; 89% B117 UK; 55% SA (94% B1351)
Sputnik V	Ad26 and Ad5 adenovirus/DNA	2	NAbs; IFN-γ secretion PMBCs, cellular	~14964	100%	100% (20 in placebo; 0 vaccine)	91.6%

Fig. 1. Description of six SARS-Cov-2 vaccine clinical studies (adapted from figure provided by Dr Monica Gandhi,[12] used with permission).

Table 1. Description of six SARS-Cov-2 vaccines against variants

	Reduction of neutralising activity in laboratory assays	Clinical efficacy against the B.1.351 variant	Clinical efficacy against ancestral variant
Pfizer	3 - 42×	Unknown	95%
Moderna	6 - 28×	Unknown	94.1%
AstraZeneca	3.5 - 21×/undetectable	10% (mild to moderate)	70.4%
Gamaleya (Sputnik-V)	Unknown	Unknown	91.6%
Johnson & Johnson	Pending	64% (moderate to severe) 82% (severe)	72% (moderate to severe disease)
Novavax	Pending	49% (including HIV; mild to moderate) 60% (excluding HIV; mild to moderate) 100% (severe)	89%
Sinopharm	1.6×	Unknown	79 - 86%
Sinovac	Unknown	Unknown	50.4%

and lockdowns on the economy.[16-18] SA lost ~8.2% (ZAR389 billion) of its gross domestic product in 2020 as a result of the COVID-19 pandemic. The cost (depending on which vaccine we use) of vaccinating everyone who needs it, is between ZAR8.6 and ZAR16.4 billion.[18]

Finally, sending the AZ vaccine to other African countries raises deep ethical concerns. The B.1.351 variant has been detected throughout Africa and may be responsible for the devastating second wave many countries have just experienced.[19,20] If the SA authorities truly believed that the AZ vaccine did not work, why was it sold on to the African Union, and why would they purchase it?

Arguments about undermining vaccine confidence by not rolling out the perfect vaccine are misguided in terms of public health. SARS-CoV-2 spreads quickly, with unpredictable waves but predictable consequences. Speed of the vaccination programme is far more important than getting the perfect vaccine. The 'abundance of caution' argument ventured by members of the SA government, the MAC-Vac and European governments, when dealing with efficacy and recent reported thrombotic side-effects of the AZ vaccine, has already seen the vaccine labelled 'second best', with reports of AZ-specific vaccine hesitance from around the globe. To be clear: the AZ vaccine is safe, and based on all known information, will be sufficiently effective in stopping the endpoints we care about most – hospitalisation and death.

We understand that a decision like this is complex, but as the reasoning behind it has not been made public, we are at a loss to explain the government's action. Politicians and advisory boards need to be transparent and explain decisions, and, if necessary, reverse them. If the NDoH, the MAC-Vac or the regulator have access to new information, this needs to be made public. Transparency is critical to trust in public health. Currently, SA has misapplied standards hampering the rollout of a vital and available tool to mitigate the epidemic. Moreover, it has gone against guidance from the WHO.[2] We do not have the luxury of choice or time. All the vaccines provide

better protection against severe disease than against mild disease. The AZ vaccine should be regarded as sufficient to prevent at least a substantial proportion of the most severe health outcomes of SARS-CoV-2 infection until data are produced to the contrary. Rapidly rolling out COVID-19 vaccine to our population at risk of severe disease and death is the most important strategic intervention to save lives, livelihoods and SA's health system and reducing the devastating effects of a third wave of COVID-19.

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