

VACCINE STRATEGY

Sisonke phase 3B open-label study: Lessons learnt for national and global vaccination scale-up during epidemics

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Sisonke is a multicentre, open-label, single-arm phase 3B vaccine implementation study of healthcare workers (HCWs) in South Africa, with prospective surveillance for 2 years. The primary endpoint is the rate of severe COVID-19, including hospitalisations and deaths. The Sisonke study enrolled and vaccinated participants nationally at potential vaccination roll-out sites between 17 February and 26 May 2021. After May 2021, additional HCWs were vaccinated as part of a sub-study at selected clinical research sites. We discuss 10 lessons learnt to strengthen national and global vaccination strategies: (i) consistently advocate for vaccination to reduce public hesitancy; (ii) an electronic vaccination data system (EVDS) is critical; (iii) facilitate access to a choice of vaccination sites, such as religious and community centres, schools, shopping malls and drive-through centres; (iv) let digitally literate people help elderly and marginalised people to register for vaccination; (v) develop clear 'how to' guides for vaccine storage, pharmacy staff and vaccinators; (vi) leverage instant messaging platforms, such as WhatsApp, for quick communication among staff at vaccination centres; (vii) safety is paramount – rapid health assessments are needed at vaccination centres to identify people at high risk of serious adverse events, including anaphylaxis or thrombosis with thrombocytopenia syndrome. Be transparent about adverse events and contextualise vaccination benefits, while acknowledging the small risks; (viii) provide real-time, responsive support to vaccinees post vaccination and implement an accessible national vaccine adverse events surveillance system; (ix) develop efficient systems to monitor and investigate COVID-19 breakthrough infections; and (x) flexibility and teamwork are essential in vaccination centres across national, provincial and district levels and between public and private sectors.

S Afr Med J 2022;112(5b):375-383. <https://doi.org/10.7196/SAMJ.2022.v112i5b.16098>

The COVID-19 pandemic, caused by SARS-CoV-2, has had a devastating effect globally. By 30 August 2021, 216 million COVID-19 cases had been confirmed worldwide, resulting in >4 million deaths.^[1] South Africa (SA), which houses 0.8% of the world's population,^[2] accounted for 1% and 1.5% of reported global COVID-19 cases and deaths, respectively.^[1-3] By the end of August 2021, SA was well into the third COVID-19 wave.^[4] During the first and second waves, dramatic increases in hospitalisations and pressure on the healthcare system led to excess deaths estimated at 2 - 3 times higher than reported.^[5] The second and third waves were fuelled by the beta and delta variants that were multiple times more transmissible than the ancestral strain of the virus.^[6]

Vaccination, alongside non-pharmaceutical interventions, is a key pillar to control the COVID-19 pandemic. Almost 100 COVID-19 vaccines are at various stages of clinical development and 6 have received emergency use listing or prequalification.^[7] These vaccines are based on the prototype Wuhan strain and primarily target the

SARS-CoV-2 spike protein.^[8] Efficacy of 94 - 95% has been reported from phase 3 trials for the messenger RNA (mRNA) vaccines (BNT162b2 and mRNA-1273), commonly known as the Pfizer BioNTech and Moderna vaccines,^[7,9,10] with 117 and 81 number needed to vaccinate to prevent 1 case of COVID-19, respectively. Efficacy of 22 - 92% has been reported for the viral vector vaccines (ChAdOx1, Gam-COVID-Vac and Ad26.COV2.S), commonly known as AstraZeneca, Sputnik V and Johnson & Johnson (J&J), against moderate-to-severe COVID-19 (Table 1).^[11-13] For the inactivated COVID-19 vaccines, efficacy against symptomatic disease was 51% for CoronaVac and 79% for Sinopharm ≥14 days after the second dose. Data on the effectiveness of COVID-19 vaccines in real-life settings are emerging (Table 1).^[14-16]

In January 2021, the SA government aimed to immunise 40 million individuals against COVID-19 by the end of 2021, starting with the ChAdOx1 nCoV-19 vaccine.^[17] The national vaccination roll-out was paused in February 2021 after reports of low efficacy of the ChAdOx1

Table 1. Vaccine types, efficacy, effectiveness and storage

Vaccine trade name	Vaccine production technology	Doses and population (country)	Efficacy	Estimated NNV ^[7]	Effectiveness against alpha, beta and delta variants	Storage times and conditions
Moderna ^[9,14]	mRNA	2 doses 28 days apart Population USA, N=30 351 age 18 - <65 yrs not at risk age 18 - <65 yrs at risk age >65 yrs	94.1% (95% CI 89.3 - 96.8) efficacy against symptomatic COVID-19 with onset ≥14 days after the 2nd dose among participants who were seronegative at baseline 95.2% (95% CI 91.2 - 97.4) efficacy with onset <14 days after 1st dose 93.6% (95% CI 88.6 - 96.5) efficacy when SARS-CoV-2-seropositive participants at baseline were included in the analysis 100% efficacy against severe COVID-19	81	Canada ^[14] Alpha - partial vaccination (≥14 days after 1st dose): 83% (95% CI 80 - 86) effective against symptomatic infection Alpha - full vaccination (≥7 days after 2nd dose): 92% (95% CI 86 - 96) Beta - partial vaccination: 77% (95% CI 69 - 92); 60% (95% CI 52 - 67) Beta - full vaccination: 84% (95% CI 69 - 92) Delta - partial vaccination: 2% (95% CI 57 - 82)	6 months at -20°C 30 days with refrigeration
Pfizer-BioNTech ^[10,14,16]	mRNA	2 doses 42 days apart	95% efficacy ≥7 days after 2nd dose, including participants >65 years old Laboratory-based testing demonstrated that antibodies neutralised the beta variant with a 3-fold decrease in titre	117	Canada ^[14] Alpha - partial vaccination: 66% (95% CI 64 - 68) Alpha - full vaccination: 89% (95% CI 86 - 91) Beta - partial vaccination: 60% (95% CI 52 - 67) Beta - full vaccination: 84% (95% CI 69 - 92) Delta - partial vaccination: 56% (95% CI 45 - 64) Delta - full vaccination: 87% (95% CI 64 - 95) Israel ^[16] (adjusted estimates of vaccine effectiveness at ≥7 days after 2nd dose) 95.3% (95% CI 94.9 - 95.7) against SARS-CoV-2 infection 91.5% (95% CI 90.7 - 92.2) against asymptomatic SARS-CoV-2 infection 97.0% (95% CI 96.7 - 97.2) against symptomatic COVID-19 97.2% (95% CI 96.8 - 97.5) against COVID-19-related hospitalisation 97.5% (95% CI 97.1 - 97.8) against severe or critical COVID-19-related hospitalisation 96.7% (95% CI 96.0 - 97.3) against COVID-19-related death	Freezer storage at -70°C 31 days with refrigeration at 2 - 8°C

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Table 1. (continued) Vaccine types, efficacy, effectiveness and storage

Vaccine trade name	Vaccine production technology	Doses and population (country)	Efficacy	Estimated NNV ⁽⁷⁾	Effectiveness against alpha, beta and delta variants	Storage times and conditions
Oxford Astra-Zeneca ^(12,14)	Viral vector	2 doses 4 weeks apart Population, N=23 848 across 4 studies n=1 077 in COV001 (UK), n=10 673 in COV002 (UK), n=10 002 in COV003 (Brazil), n=2 096 in COV005 (SA)	70.4% (95.8% CI 54.8 - 80.6) efficacy against symptomatic COVID-19 ≥14 days after 2nd dose in all low-dose, SD and SD:SD recipients 62.1% (95% CI 41.0 - 75.7) efficacy in SD recipients, whereas 90.0% (95% CI 67.4 - 97.0) efficacy in those who received a low dose as their 1st dose In SA, efficacy against the beta variant for mild-to-moderate COVID-19 ≥14 days after 2nd dose was 21.9% (95% CI 49.9 - 59.8) and 10.6% (95% CI -66.4 - 52.2) among previously COVID-19-seronegative and COVID-19-seropositive participants, respectively ⁽¹⁸⁾	78	Canada ⁽¹⁴⁾ Alpha - partial vaccination (≥14 days after 1st dose): 64% (95% CI 60 - 68) Beta - partial vaccination: 48% (95% CI 28 - 63)	Refrigeration at 2 - 8°C
Johnson & Johnson ⁽¹³⁾	Viral vector	Single dose, N=43 783 received vaccine or placebo Per-protocol population, N=39 321 SARS-CoV-2-negative participants, n=19 630 received Ad26, COV2.S, n=19 691 received placebo Participants recruited across 6 countries in Latin America, USA and SA In SA, n=3 286 received Ad26, COV2.S, n=3 290 received placebo	67% and 66% efficacy against moderate to severe-critical COVID-19, with onset at least 14 and 28 days after vaccination, respectively 77% and 85% efficacy against severe-critical COVID-19, with onset at ≥14 days and ≥28 days, respectively In SA, efficacy predominantly against the beta variant was 52% and 64% against moderate to severe-critical COVID-19, with onset at least 14 and 28 days after vaccination, respectively Efficacy against severe-critical COVID-19 was 73% and 82%, with onset at least 14 and 28 days after vaccination, respectively	84	None published yet as of 31 August 2021	Freezer storage for 2 years at -20°C 3 months with refrigeration at 2 - 8°C

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Table 1. (continued) Vaccine types, efficacy, effectiveness and storage

Vaccine trade name	Vaccine production technology	Doses and population (country)	Efficacy	Estimated NNV ^[7]	Effectiveness against alpha, beta and delta variants	Storage times and conditions
Sputnik V/Gam-COVID ^[11]	Viral vector: recombinant replication-deficient adenovirus (rAd)-based vaccines	2 doses 3 weeks apart 1st dose (rAd26 S) and 2nd dose (rAd5 S), both of which carry the gene for SARS-CoV-2 full-length glycoprotein S, uses heterologous prime-boost vaccination approach N=21 977 randomised (all participants from Russia)	First COVID-19 occurrence >21 days after 1st dose - 91.6% (95% CI 8.6 - 95.2) First COVID-19 occurrence ≥28 days after 2nd dose - 91.1% (95% CI 83.8 - 95.1); 100% (95% CI 94.4 - 100) efficacy against severe COVID-19	108	None published yet	Two forms of the vaccine - liquid (stored at -18°C) and freeze-dried (stored at 2 - 8°C) [†]
Sinovac-CoronaVac (COVID-19) [‡]	Inactivated virus	2 doses 2 - 4 weeks apart	2 doses at a 14-day interval had 51% efficacy against symptomatic SARS-CoV-2 infection, 100% against severe COVID-19, and 100% against hospitalisation ≥14 days after 2nd dose	-	None published yet	Refrigeration at 2 - 8°C; may remain stable for up to 3 years
Sinopharm COVID-19 [§]	Inactivated virus	2 doses 3 - 4 weeks apart	79% efficacy against symptomatic SARS-CoV-2 infection ≥14 days after 2nd dose 79% efficacy against hospitalisation	-	None published yet	Refrigeration at 2 - 8°C

NNV = number needed to vaccinate to prevent 1 more case of COVID-19^[7] mRNA = messenger RNA; CI = confidence interval; SD = standard dose; SA = South Africa.
[†]Vaccine efficacy is generally reported as a relative risk reduction (RRR), i.e. the ratio of attack rates with and without a vaccine, expressed as 1 relative risk. RRR should be seen against the background risk of being infected and becoming ill with COVID-19, which varies between populations and over time. RRR considers only participants who could benefit from the vaccine. The absolute risk reduction (ARR) is the difference between attack rates with and without a vaccine and considers the whole population. ARR is also used to derive an estimate of vaccine effectiveness, which is the NNV to prevent 1 more case of COVID-19 as 1/ARR.
[‡]In this study, the liquid form was used. Storage at 2 - 8°C has been approved by the Ministry of Health of the Russian Federation.
[§]Source: <https://www.who.int/news-room/feature-stories/detail/the-sinopharm-covid-19-vaccine-what-you-need-to-know>

nCoV-19 against the beta variant in SA.^[18] The Ad26.COV2.S J&J vaccine was tested during the ENSEMBLE phase 3 randomised, double-blind, placebo-controlled study, with almost 44 000 adults across 8 countries, including 7 000 participants enrolled and followed up at 32 sites in SA.^[13] Data were gathered between August and December 2020. The analysis (cut-off date 22 January 2021) found that the vaccine was safe and the SA data demonstrated protection against the beta variant and severe disease and hospitalisation (Table 1). Given these findings, the vaccine was considered for the national roll-out programme.^[13]

Ad26.COV2.S is a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus type 26 (Ad26) vector, constructed to encode the SARS-CoV-2 spike (S) protein. This single-dose Ad26.COV2.S vaccine is estimated to remain stable for 2 years at -20°C, at least 3 months of which can be at temperatures of 2 - 8°C. This permits seamless distribution using the existing vaccine supply chain channels in low- and middle-income countries, such as SA.

Methods

Sisonke is a multicentre, open-label, single-arm phase 3B implementation study of healthcare workers (HCWs) in SA (ClinicalTrials.gov number, NCT04838795), with prospective surveillance for endpoints for 2 years. It was implemented while waiting for registration of the Ad26.COV2.S vaccine by the South African Health Products Regulatory Authority (SAHPRA). The study sought to vaccinate 500 000 HCWs ahead of the third COVID-19 wave in SA.

The primary endpoint was the rates of severe COVID-19 (hospitalisations and death) among vaccinated HCWs compared with the general unvaccinated SA population. This study is led by the South African Medical Research Council (SAMRC). The protocol was designed to be pragmatic and as near to real-world vaccination roll-out as possible.

The study began in 18 hospital-based vaccination sites overseen by 16 clinical research sites, before expanding to a total of 122 urban and rural vaccination sites located across all 9 SA provinces, overseen by 43 clinical research sites. The last vaccination was administered on 12 August 2021 through the Sisonke sub-study. HCWs were defined as 'all people engaged in actions whose primary intent is to enhance health.'^[19] For the first 2.5 months of the Sisonke study, patients-facing HCWs who worked on COVID-19 wards, intensive care units and operating theatres were prioritised for study enrolment. From 11 May 2021, the HCW definition expanded to non-patient-facing HCWs, support and administrative staff, health research staff, community health workers, staff working in care homes, funeral workers and registered traditional health practitioners.

In order to participate in the Sisonke study, HCWs had to firstly register on the national electronic vaccination data system (EVDS). Secondly, they had to consent to study participation after reading an online consent form and answering 6 questions to test their understanding of the study. Thirdly, they had to consent to vaccination after a screening evaluation at the vaccination centre. The date of screening was typically the date of vaccination.

Eligible HCWs were ≥18 years of age, in the private or public service, who were willing and able to comply with the vaccination plan and other study procedures, and who were capable of providing electronic or paper-based signed informed consent. Participants who reported breastfeeding at the time of enrolment were included up until 13 April 2021, when SAHPRA requested their exclusion pending more safety data. SAHPRA granted permission to re-include breastfeeding women on 28 April 2021. Special vaccine advocates, including the president and deputy-president of SA, were also included.

Exclusion criteria were: (i) any significant acute or chronic medical condition that in the opinion of the principal investigator/designee made the participant unsuitable for enrolment in the study, or jeopardised the safety or rights of the participant; and (ii) current participation in any other research studies that would interfere with the objectives of this study. Participants who reported being pregnant at time of enrolment or planning to conceive within 3 months were excluded from the study, but were later invited to participate in the Sisonke sub-study. For HCWs with a history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine, eligibility was determined after consultation with a protocol safety review team (PSRT). Following a pause called by the Food and Drug Administration (FDA) on 13 April 2021 to review unusual clotting events in vaccine recipients in the USA, participants with a history of major venous or arterial thrombosis with thrombocytopenia and those with a history of heparin-induced thrombocytopenia were excluded. Participants with a chronic history of severe clotting disorders were only included after approval by the PSRT. Vaccination within 14 - 90 days with other vaccines were not exclusionary, but were discussed with the PSRT or the principal investigators of the study. A 2-week gap had to be allowed between influenza vaccination and COVID-19 vaccination.

Research staff on the Sisonke study worked in collaboration with local designated

vaccination sites. Sisonke study staff supported and trained vaccination site staff on standardised study procedures.

All vaccinated participants were entered into the national COVID-19 vaccination register through EVDS. The single-dose vaccine was administered to all participants as an intramuscular injection in the deltoid region of their non-dominant arm. All participants received a single dose of Ad26.COV2.S comprising 5×10^{10} viral particles/mL.

Results, lessons learnt and discussion

The Sisonke study enrolled and vaccinated 496 424 HCWs (Table 2). The majority of vaccinees were from Gauteng, Western Cape and KwaZulu-Natal provinces, in keeping with national population distributions. Approximately 28 200 vaccinations were administered in remote parts of the Eastern Cape and Northern Cape provinces.

We highlight 10 challenges and lessons learnt (Table 3) using a framework that focuses on creating a system to deliver and report vaccinations and to support vaccinees (Fig. 1). We also highlight implications for any roll-out of vaccines during infectious disease epidemics or pandemics (Table 3).

Lesson 1: Consistently advocate for vaccination to reduce public hesitancy

During the study period there were reports of vaccine hesitancy in the mainstream and popular media relating to adverse events. We realised that a key advocacy message was that severe adverse reactions to vaccination are rare and can be managed, but severe COVID-19 is life threatening. In the Sisonke study, such vaccine-related questions were largely addressed through appropriate clear messaging and peer education using webinars, posters/leaflets, social media

engagements and interviews on local, national and international news outlets. It was important for the Sisonke investigators and team to respond to queries arising from potential participants or stakeholders, and to dispel myths and misunderstandings with regard to COVID-19 vaccines.

Communicating risks became more complex when the rare blood-clotting condition was first reported. Sisonke messaging explained that headaches during the first 3 days could be managed with reassurance, but needed to be taken more seriously if severe with an onset between 4 and 20 days after vaccination or associated with blurred vision, weakness or difficulty speaking.

Table 2. Location, age and number (% of healthcare workers vaccinated in the Sisonke study)

Characteristics	n (%)
Province	496 424 (100)
Eastern Cape	60 477 (12.2)
Free State	24 347 (4.9)
Gauteng	135 140 (27.2)
KwaZulu-Natal	94 374 (19.0)
Limpopo	33 988 (6.8)
Mpumalanga	21 520 (4.3)
North West	23 416 (4.7)
Northern Cape	9 452 (1.9)
Western Cape	93 710 (18.9)
Age, years	
18 - 19	2 461 (0.5)
20 - 29	73 374 (14.8)
30 - 39	140 564 (28.3)
40 - 49	142 339 (28.7)
50 - 59	100 746 (20.3)
60 - 69	30 741 (6.2)
70 - 79	5 268 (1.1)
80 - 89	719 (0.1)
Still being cleaned	212 (0.0)

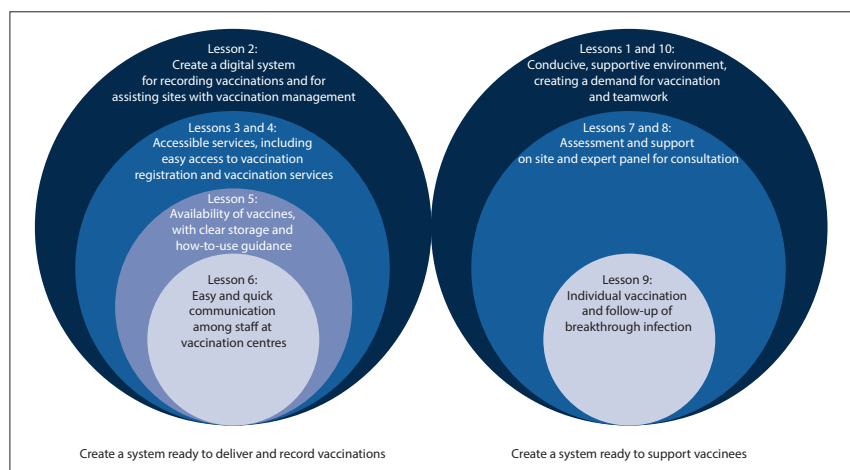


Fig. 1. Conceptual framework for vaccination scale-up during pandemic.

Table 3. Ten lessons learnt from the Sisonke study that could inform any rapid national roll-out of vaccinations during pandemics

Challenges	10 lessons learnt	Implication for any national roll-out of vaccination during infectious disease pandemics
Social media were abuzz with information regarding the dangers of vaccination	1. Consistently advocate for vaccination to reduce public hesitancy	Vaccinations should not be missed, unless there is a true contraindication. Webinars, posters/leaflets, social media engagements and interviews on local, national and international news outlets need to be responsive to community concerns, and available for engagement
Paper-based forms are easily lost Real-time data entry is needed for daily tracking of vaccination coverage, vaccines administered and vaccine supplies	2. An EVDS is of critical importance	An electronic system is an important tool. Busy vaccination centres can use EVDS scheduling to avoid overcrowding
At the start of the Sisonke study, sites were inundated with crowds of healthcare workers seeking vaccination. This presented challenges for social distancing and resulted in long waiting periods. Additionally, staff from non-vaccinating facilities had to be transported to vaccination sites	3. Facilitate access to a choice of vaccination sites, such as religious and community centres, schools, shopping malls and drive-through centres	Religious and community leaders should be involved as vaccine advocates, and school/religious/community halls, malls and other easily accessible places should be used as vaccination sites. Where possible, drive-through vaccination sites should be set up, with parking for medical oversight during the 15-minute post-vaccination observation period
Registering on EVDS was challenging, particularly for healthcare workers who were not very digitally literate	4. Let digitally literate people help elderly and marginalised people register for vaccination	Communication material should illustrate how to register on EVDS, and various options should exist for vaccine registration, including walk-in registrations
Vaccines, whether used as an investigational product or as commercial doses, need to be stored and drawn up stringently	5. Develop clear 'how to' guides for vaccine storage, pharmacy staff and vaccinators	Develop and distribute clear training material and standardised operating procedures
Information changed quickly, and questions arose that needed immediate resolution; therefore, study staff needed a quick platform to communicate changes in real time	6. Leverage instant messaging platforms, e.g. WhatsApp, for quick communication among staff at vaccination centres	Develop communication materials for staff that can be shared through social media platforms to notify them of any changes to the vaccine programme
To reduce the risk of post-vaccination adverse events, health interviews are needed before vaccination. Additionally, there was a flurry of reports about rare or less common vaccination adverse events in the media, which caused vaccine hesitancy and confusion and needed contextualisation	7. Rapid health assessments are needed at vaccination centres to identify people at high risk of serious adverse events. Be transparent about adverse events to the public and contextualise vaccination benefits, while acknowledging the small risks	Apply checklists to identify high-risk people when doing COVID-19 screening. Develop clear communication about the risk-benefit ratio of vaccination. Expand options for reporting adverse events
After vaccination, vaccinees had questions regarding rashes, headaches and other adverse events	8. Provide real-time, responsive support to vaccinees post vaccination and implement an accessible national vaccine adverse events surveillance system	Ensure that the call centre operates 24/7 and is able to attend to thousands of administrative and provider queries. Follow up people with side-effects until all symptoms have resolved
Breakthrough infections occurred, but these needed to be carefully investigated to ascertain timing after vaccination and severity	9. Develop efficient systems to monitor and investigate COVID-19 breakthrough infections	Set systems in place to document and investigate breakthrough infections to establish temporality and causality
Given the rapidity with which vaccinations occurred, plans needed to be flexible and responsive, with constant review	10. Flexibility and teamwork are essential in vaccination centres, across national, provincial and district levels and between public and private sectors	Encourage teamwork and local solutions at national, provincial, district and facility level, and by public-private sector collaborations to reach all cadres of healthcare workers, including nurses, doctors, allied health professionals, community health workers, traditional health practitioners and all health sector support staff

EVDS = electronic vaccination data system.

It is, however, important to communicate the risk of these events alongside the risks of COVID-19, so that people can make informed choices regarding vaccination.

In national vaccine roll-outs every vaccinee and HCW needs to be a vaccine advocate in their circles of influence.

Lesson 2: An electronic vaccination data system is critical

Paper forms were used to document vaccinations at some sites, often resulting in a delay in EVDS data capture. An EVDS is an important tool for real-time documentation of individual vaccinations and tracking of district, provincial and national progress. An EVDS also

facilitates scheduling and real-time communication with vaccinees, recording vaccinee characteristics, ensuring standardisation of implementation and data quality. Critically, Sisonke enabled the National Department of Health (NDoH) to test the implementation of the EVDS. The electronic system should ensure that each person is linked with an occupation and place of work, which assists with monitoring the success of the vaccine roll-out.

Busy vaccination centres should use EVDS scheduling to avoid over-crowding, and queue marshals can be employed to monitor that vaccinees abide by their EVDS appointment time and to assist with social distancing.

Lesson 3: Facilitate access to a choice of vaccination sites, such as religious and community centres, schools, shopping malls and drive-through centres on weekdays and weekends

The limited number of vaccination sites meant that queues were long and HCWs had to wait, sometimes for ~3 hours, to be vaccinated. A key lesson was that vaccination sites should be easily accessible, using community centres, religious centres/halls, schools, shopping malls and drive-through centres, with parking space for the 15 minutes of observation. Partnering with local religious and community leaders is essential to achieve this.

Lesson 4: Let digitally literate people help elderly and marginalised people to register for vaccination

During the Sisonke study, registration for vaccination occurred mainly through a web-based portal. We learnt that registration should be allowed through various portals and systems, including WhatsApp and short message service (SMS), and that digitally literate people should help elderly and marginalised people to register for vaccination so that the digital divide does not exclude anyone. The opening of vaccination sites to walk-ins during the final week demonstrated that many HCWs had not refreshed their details or had missed SMS notifications. This situation emphasised the importance of allowing walk-ins during national vaccine roll-outs to maximise vaccine uptake.

Lesson 5: Develop clear 'how to' guides for vaccine storage, pharmacy staff and vaccinators

Nurses have prepared and administered vaccines for decades, but there has not been a recent vaccination campaign of this scale and complexity during a pandemic. COVID-19 vaccines are provided as small-volume injections. Ensuring that the volume is correctly drawn up is critical.

Cold-chain management also needs careful monitoring and accountability.

The Ad26.COVS.2 and Pfizer-BioNTech vaccines have varying reconstitution and storage requirements. Pfizer must be reconstituted by injecting saline into the vial, neither can be shaken, needles cannot be changed between drawing up a dose and injecting it, and microdrops remaining in the needle nib increase wastage and risk sub-optimal dosing. The reconstituted vaccine must be stored between 2°C and 25°C and used within 6 hours of dilution. Consequently, close communication is needed between staff who reconstitute vaccine and staff who manage the vaccine queues, to prevent vaccine wastage.

The Sisonke protocol team realised the need for detailed resources on how to draw up each dose.^[20] Study training therefore provided quality assurance, and a 3-step volume verification process was instituted to ensure that every dose counted. Furthermore, each dose was quality checked before leaving the pharmacy, and there was little wastage (<1%).

Allocating this process to dedicated trained teams and expanding the capacity of these teams optimised efficiency at vaccination centres and should be continued during any large-scale vaccination roll-out. Many of the processes and tools developed for Sisonke have already been adapted and are being used in the national COVID-19 vaccination programme.

Lesson 6: Leverage instant messaging platforms, such as WhatsApp, for quick communication among staff at vaccination centres

Given the nature of COVID-19, information changed regularly. Providing factual and useful information to vaccination sites is key to enhance efficiency at such centres and allay concerns. We realised the need to distribute a wide range of tools from job aids, checklists, press statements and posters through WhatsApp groups to keep vaccination staff updated. These WhatsApp groups enabled principal investigators to rapidly implement changes on the ground and redistribute vaccine doses to avoid wastage, and allowed investigators and vaccination centre staff to support each other during long days and weeks.

Lesson 7: Safety – health assessments at vaccination sites and transparency regarding adverse events

Although severe allergic reactions to COVID-19 vaccines are rare, we realised that real-time rapid health assessments are needed at vaccination centres to identify people at risk of severe reactions. These assessments are important to identify those with a history of severe allergic reactions/anaphylaxis, who need to be administered medication before vaccination under medical supervision at specialised centres. Those with a history of allergy have to be identified and observed for 30 rather than 15 minutes.

In the Sisonke study, the rate of reported non-serious and serious adverse events with vaccination was low, with the majority of reported events being manifestations of mild-to-moderate reactogenicity (81%), while thromboembolic events occurred mainly in persons with risk factors for thromboembolism.^[21]

Education and communication regarding these adverse events are needed early, frequently and honestly, and should juxtapose the benefits v. the risks of vaccination. All too often risks were communicated separately from the benefits of vaccination, generating fear and confusion, which was particularly true of the risk of thrombosis with thrombocytopenia syndrome related to vaccine administration. The study team realised that weighing risks against benefits is contextual. While the USA had the luxury of being at a far-advanced stage of their roll-out, with 37% of their population vaccinated by 13 April 2021 when the FDA recommended a pause, the proportion of the population vaccinated in SA was 0.5% (just <300 000), with a third wave rapidly approaching. Reciprocal licensure and safety arrangements must be considered against the contextual risk of suspending vaccination programmes because of rare events, despite limited access to vaccine options. For example, reports indicated that France and Poland did not suspend their use of Ad26.COVS.2 while safety data were under review, providing an important precedent for determining policy based on vaccination coverage and community transmission.^[22] As with movement restrictions, decisions informed by local data are advisable.

Lesson 8: Provide real-time, responsive support to vaccinees after vaccination

Adverse event reporting systems that are easily accessible, easy to use and data free are needed to maximise adverse event reporting and follow-up. In the Sisonke study, adverse event reporting included text

message-based electronic reporting, 24/7 toll-free call centres, website links, health facility-based reporting, as well as encouragement of spontaneous case reporting.

The study team established an effective safety monitoring system based on both active (when the team follows up directly with vaccinees) and passive (when vaccinees are asked to report side-effects to the team) reporting.

A national roll-out should include an active national vaccine adverse event surveillance system and a safety desk that operates 24/7 and is responsive to vaccinees' concerns.

Lesson 9: Develop efficient systems to monitor and investigate COVID-19 breakthrough infections and deaths

During and after vaccination, monitoring and investigating breakthrough infections (BTIs) and deaths are critical to understand the emergence of new variants. We realised the need for a national BTI consortium that brings together teams from the National Institute for Communicable Diseases, the National Health Laboratory Service, the SAMRC Burden of Disease Research Unit, epidemiologists and private laboratories to ensure complete documentation of disease, hospitalisations and deaths, as well as viral genetic information. Furthermore, the Sisonke study showed that each severe BTI and death needed investigation and review by a team of experts to confirm the occurrence and establish temporality (in relation to vaccination or COVID-19). For any national roll-out, similar systems are needed, and should be led by key national stakeholders and experts.

Lesson 10: Flexibility and teamwork are essential in vaccination centres, across national, provincial and district levels and between public and private sites

Sisonke's mandate was to reach as many HCWs as possible within 3 months with the research-allocated 500 000 doses of the Ad26.COV2.S vaccine imported for this purpose. This outreach was achieved through a public-private partnership in many sites, with the private sector either serving as vaccination centres or providing staff as vaccinators, pharmacists or syringe fillers.

Nothing was off limits for vaccination centre staff who engaged with health department teams, carried fridges, oversaw meticulous preparation of doses and consent processes and managed side-effects and reporting.

Conclusion

The Sisonke study team and collaborators made history by moving from the ENSEMBLE phase 3 trial results to the large-scale phase 3B study in <2 months. The Sisonke study is an example of what is possible when political will, science, hard work, partnership and a strong desire to act come together to serve public health.

Declaration. None.

Acknowledgements. South African Medical Research Council (study sponsor and oversight), Janssen Vaccines and Prevention (supply and transport of the study product to South Africa), National Department of Health, overseeing ethics committees, South African Health Products Regulatory Authority, Biocair, vaccine centres (hospitals), clinical research site principal investigators and teams, including the following: S Badal-Faesen (Themba Lethu HIV Research Unit and Clinical HIV Research Unit (CHRU)), S Barnabas (FAM-CRU), L G Bekker and S Mahoney

(Desmond Tutu HIV Foundation-Emavundleni Research Centre), L Burgess (TREAD Research), W Brumskine (Aurum Institute Rustenburg Clinical Research Centre), R Dawson (University of Cape Town Lung Institute), A Diacon (TASK Central), T Dubula (Nelson Mandela Academic Clinical Research Unit), J Engelbrecht (Dr J M Engelbrecht Clinical Trial Site), K Gill (Desmond Tutu Health Foundation (DTHF) Masiphumelele Clinic), C Grobbelaar (Aurum Institute Clinical Research Centre Pretoria), L Hellstrom (Be Part-Yoluntu Centre), N Hussen (Worthwhile Clinical Trials), C Innes (Aurum Institute Klerksdorp Clinical Research Centre), N Joseph (Peermed CTC (Pty) Ltd T/A MERC), S Kassim (Desmond Tutu Health Foundation Clinical Trials Unit), S Kotze (Synexus Stanza Research Centre), P Kotze (Qhakaza Mbokodo Research Clinic), E Lazarus (Perinatal HIV Research Unit), J Lombard (Joshua Research), A Luabeya (South African Tuberculosis Vaccine Initiative (SATVI), Brewelskloof Hospital), D Makhaza (CAPRISA Vulindlela Clinic), R B Maboa (Ndlovu Research Centre), M Malahela (Setshaba Research Centre), D Malan (PHOENIX Pharma (Pty) Ltd), M Mamba (CRISMO Bertha Gxowa Research Centre), K Mngadi (Aurum Institute Tembisa Clinical Research Centre), L Naidoo (Chatsworth Clinical Research Site, SAMRC), N Naicker (CAPRISA eThekweni Clinic), V Naicker (Tongaat Clinical Research site, SAMRC), M Nchabaleng (Mecru Clinical Research Unit), T Nielsen (Aurum Institute), F Patel (Wits RHI-Shandukani Research), F Petrick (Mzansi Ethical Research Centre), E Spooner (Botha's Hill Clinical Research site, SAMRC), D Urbach (Synexus Helderberg Clinical Research Centre), E van Nieuwenhuizen (Synexus SA Watermeyer Clinical Research Centre), A Ward (Ekhayavac TB Vaccine Trial Unit/Khayelitsha CRS (CIDRI UCT)).

Author contributions. GG, L-GB, AEG and NG conceptualised the Sisonke study. AEG wrote the first draft of the manuscript. All authors contributed to all sections of the article and reviewed the draft manuscript.

Funding. The Sisonke study is funded by the South African Medical Research Council, with funds received from National Treasury through the South African National Department of Health and by the Solidarity Fund, the ELMA Vaccines and Immunisation Foundation, the Michael and Susan Dell Foundation and the Bill and Melinda Gates Foundation.

Conflicts of interest. None.

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Accepted 29 November 2021.