Safety of a second homologous Ad26.COV2.S vaccine among healthcare workers in the phase 3b implementation Sisonke study in South Africa

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Abstract

The Sisonke 2 study provided a homologous boost at least 6 months after administration of the priming dose of Ad26.COV2.S for healthcare workers enrolled on the Sisonke phase 3b implementation study.

Safety monitoring was via five reporting sources: (i.) self-report through a web-link; (ii.) paper-based case report forms; (iii.) a toll-free telephonic reporting line; (iv.) healthcare professionals-initiated reports; and (v.) active linkage with National Disease Databases.

A total of 2350 adverse events were reported by 2117 of the 240 888 (0.88%) participants enrolled; 1625 of the 2350 reported events are reactogenicity events and 28 adverse events met seriousness criteria. No cases of thrombosis with thrombocytopaenia syndrome were reported; all adverse events including thromboembolic disorders occurred at a rate below the expected population rates apart from one case of Guillain Barre Syndrome and one case of portal vein thrombosis.

The Sisonke 2 study demonstrates that two doses of Ad26.COV2.S is safe and well tolerated; and provides a feasible model for national pharmacovigilance strategies for low- and middle-income settings.

Keywords: Ad26.COV2.S; Sisonke study; Vaccine safety; Pharmacovigilance; Homologous boost

1. Introduction

The single dose Ad26.COV2.S vaccine was one of the first COVID-19 vaccines that became available and was widely administered in low- and middle-income settings. In February 2021, the Sisonke phase 3b open-label implementation trial offered almost 500,000 healthcare workers (HCWs) in South Africa emergency access to this vaccine. The trial has shown that the single dose was overall well tolerated [1] and effective in preventing hospitalizations and deaths during the delta and omicron waves in South Africa (SA) [2], [3].

In Sisonke, safety of the first dose of Ad26.COV2.S was assessed through self- and healthcare provider reporting of adverse events (AEs) via a study safety desk, where case reports were collated. Overall, the analysis showed that most AEs meeting International Conference on Harmonisation of Good Clinical Practice (ICH-GCP) seriousness criteria, serious adverse events (SAEs) and adverse events of special interest (AESIs) observed in the study occurred at a rate

below the expected population rates and allergic AEs were rare [4]. After the first dose four cases of Guillain-Barré syndrome (GBS) were reported, and occurred at slightly higher rates than expected in a population; in addition, two cases of thrombosis with thrombocytopaenia syndrome (TTS) were reported, one meeting the criteria of vaccine induced thrombotic thrombocytopaenia (VITT) and the second case where VITT was the most likely diagnosis [1], [5].

By September 2021, the ENSEMBLE 2 trial results were available [6], [7] which showed safety and an additional protection benefit from severe disease after a second dose of Ad26.COV2.S. Considering the safety, effectiveness and superior immunogenicity, the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) updated recommendations for the use of the Ad26.COV2.S vaccine from one to two doses [8], [9]. In response, the Sisonke study protocol team were able to offer all Sisonke participants a second dose of Ad26.COV2.S vaccine as part of the Sisonke 2 study.

The aim of the Sisonke 2 study was to assess the safety and effectiveness of a second dose of Ad26.COV2.S among Sisonke participants during the ongoing COVID-19 pandemic. Here, we report the safety of a second Ad26.COV2.S dose as a homologous boost in a real-world setting in South Africa.

2. Methods

2.1. Study participants

The Sisonke 2 study was a multi-centre, open label, single arm phase 3b implementation study among HCWs who participated in the Sisonke study. Sisonke participants who had received a single dose of Ad26.COV2.S as recorded in the South African national Electronic Vaccination Data System (EVDS) were invited for vaccination through short message services (SMS) and provided electronic consent for participation.

Sisonke participants who had been vaccinated with a first dose of Ad26.COV2.S at least six months prior were eligible to receive the second dose. Those who had received another COVID-19 vaccine after the first Ad26.COV2.S vaccine, and those with a history of heparin induced thrombocytopenia or TTS were excluded. Full eligibility criteria are shown in Supplementary Table 1. In addition, case reports of participants who experienced SAEs during the Sisonke study were reviewed by the protocol and safety review team (PSRT), which included principal investigators, safety physicians, and specialists in haematology, neurology, and clinical immunology, to ascertain safety of administering a second Ad26.COV2.S vaccination. Participants with a reported or confirmed thrombo-embolic and neurologic event after the first Ad26.COV2 dose (n = 43) were not enrolled, but recommended to receive a mRNA COVID-19 vaccine, if appropriate [10], [11], [12].

The Sisonke 2 study was conducted in collaboration with the SA National Department of Health (ClinicalTrials.gov

NCT05148845; SA Clinical Trials Registry DOH-27–112021-9038). Regulatory oversight was provided by the South African Health Products Regulatory Authority (Database Tracking

number: 20210433). Clinical research sites (CRS) obtained approval from their respective institutional human research ethics committees.

2.2. Vaccination procedures

Vaccinations were administered at designated national vaccination centres with CRS oversight to ensure that procedures align to ICH-GCP principles. Following verification of identity, eligibility and consent, a single homologous dose of 5×10^{10} viral particles of Ad26.COV2.S was administered intramuscularly into the left or right deltoid muscle. Participants were observed for 15 min, or 30 min for participants with a history of allergic reactions to vaccinations.

2.3. Safety reporting and monitoring

AEs were reported to the study database via five sources: (i.) electronic self-report through a web-link sent via SMS to participants on the day of vaccination and 14 and 21 days after vaccination; (ii.) paper-based case report forms predominantly utilised by healthcare providers at vaccination centres were scanned/emailed to the Sisonke safety desk and captured in the safety database; (iii.) telephonic reporting via a toll free number where pharmacovigilance officers captured events in the database and/or escalated specific queries to study safety medical officers; (iv.) spontaneous case reports from unsolicited communication by healthcare professionals; and (v.) linkage with National Disease Databases including the National Health Laboratory Services Corporate Data Warehouse for SARS-CoV-2 line listing, the Daily Hospital Surveillance for COVID-19 related hospitalizations database and the SA Medical Research Council Burden of Disease Unit/Home Affairs death registration list for all-cause mortality. The analysis included AEs were reported throughout the study until the data censoring date on 28 February 2022, 28 days after administration of the last vaccination in Sisonke 2.

AEs in the database were monitored daily via a manual review of the listings and a STATA code which identified events meeting ICH-GCP seriousness criteria and those listed in the Brighton Collaboration and Safety Platform for Emergency vACcines (SPEAC) Project Priority list of COVID-19 AESI. These events were flagged for follow-up by pharmacovigilance officers or safety physicians [13], [14]. Safety physicians compiled reports of SAEs and AESIs, for weekly review by the PSRT.

2.4. Statistical analysis

Counts and proportions were used for categorical variables, medians, and interquartile ranges for continuous variables. SAEs were summarised by Medical Dictionary for Regulatory Authorities System Organ Class (MedDRA - SOC) and AE preferred term. For SAEs of concern and AESIs, disproportionality analysis was conducted: The observed (O) number of reported cases was compared to the expected (E) number based on background incidence rates, and the O/E ratio with 95 % confidence interval (CI) was calculated. The 95 % CI for the O/E ratio were calculated as follows: (i) the 95 % CI of the observed number of events was calculated

assuming a chi-squared distribution, and (ii) each of the lower and upper limits of the CI in (i) were divided by the number of expected events to produce the 95 % CI for the O/E ratio. Due to lack of comprehensive contextual comparator data for our cohort, the methodology used to collate available background incidence was previously published as part of the Sisonke Safety evaluation [1] and includes a combination of the following: SA medical insurance data (thromboembolic events); the Brighton Collaboration, and European population database (TTS and neurologic disorders) [15], [16].

3. Results

A total of 477 234 HCWs who had received a single dose of Ad26.COV2.S in the Sisonke study were invited by SMS to participate in the Sisonke 2 study. Of these, 240 888 (50.5 %) received a second Ad26.COV2.S dose between 10 November 2021 and 31 January 2022. Of the Sisonke 2 participants, 178,573 (74.13 %) were female, the median age was 44 years (IQR 35–53). A total of 2350 AEs were reported by 2117 (0.88 %) participants. Females reported 1641 (77.52 %) of AEs. Most AEs were reported by participants between the ages 31–44. Table 1 shows the demographics of participants who reported AEs.

Table 1. Demographics of participants who reported AEs in the Sisonke 2 study.

Characteristic	**Reported AE N (%)**	**Total Enrolled N**
Sex		
Female	1 641 (0.9)	178 573
Male	476 (0.8)	62 315
Age median (IQR)	42 (33–51)	44 (35–53)
Age category (years)		
18–30	389 (1.1)	34 503
31–45	907 (1.0)	95 302
46–55	457 (0.7)	63 516
>55	364 (0.8)	4 756
Total	**2 117**	**240 888**

Among the 2350 AEs,1625 were common reactogenicity events and 725 were other AEs. There were 28/2 350 (1.2 %) AEs that met the ICH-GCP seriousness criteria. Of these, 25/28 (89.3 %) were reported by females with a median age of 42 years (IQR 33–51). Most SAEs fell into the following MedDRA–SOC: vascular system disorders (n = 9), immune system disorders (n = 6) and nervous system disorders (n = 6). A complete list of SAEs categorised by MedDRA-SOC and preferred term is shown in Table 2. Of the 9 vascular system AEs, 8 were thromboembolic events with the most common events being pulmonary embolism (n = 3) and cerebrovascular accident (n = 2). Of the eight cases with thromboembolic events, 7 were reported by females, with a median age of 46 years (IQR 37 – 56), and median time to onset after vaccination of 16 days (IQR 8 – 20). There was no evidence of thrombocytopaenia amongst these cases.

Table 2. Serious Adverse Events by MedDRA System Organ Class and preferred adverse event term (n = 28).

System Organ Class	N (%)	Incidence per 100 000 PY
Vascular Disorders	**9**	15.08 (6.89—28.62)
Cerebrovascular accident	2	3.35 (0.41–12.1)
Pulmonary Embolism	3	5.03 (1.04–14.69)
Portal Vein Thrombosis	1	1.68 (0.04–9.33)
Deep Vein Thrombosis	1	1.68 (0.04–9.33)
Myocardial Infarction	1	1.68 (0.04–9.33)
Elevated Blood Pressure	1	1.68 (0.04–9.33)
Thromboembolic Disorders	8	13.4 (5.79 – 26.41)
Neurological Disorders	**6**	10.05 (3.67——21.88)
Guillain-Barré Syndrome	1	1.68 (0.04–9.33)
Aseptic Meningitis	1	1.68 (0.04–9.33)
Headache	1	1.68 (0.04–9.33)
Seizure	3	5.03 (1.04–14.69)
Immune System Disorders	**4**	**6.70 (1.83–17.16)**
Allergic reaction	2	3.35 (0.41–12.1)
Severe reactogenicity symptoms requiring hospitalisation	1	1.68 (0.04–9.33)
Fibromyalgia flare	1	1.68 (0.04–9.33)
Gastrointestinal disorders	**2**	3.35 (0.41—12.1)
Obstructive pancreatitis	1	1.68 (0.04–9.33)
Omental tear	1	1.68 (0.04–9.33)
Infections and Infestations	**3**	**5.03 (1.04–14.69)**
Upper Respiratory Tract Infection	1	1.68 (0.04–9.33)
Pneumonia	1	1.68 (0.04–9.33)
Appendicitis	1	1.68 (0.04–9.33)
Injury, poisoning and procedural complications	**2**	**3.35 (0.41–12.1)**
Injection site pain	1	1.68 (0.04–9.33)
Injection site complication	1	1.68 (0.04–9.33)
Musculoskeletal and connective tissue disorders		
Costochondritis	1	1.68 (0.04–9.33)
Renal and urinary disorders		
Acute kidney injury	1	1.68 (0.04–9.33)

Two participants experienced SARS-CoV-2 infections post vaccination and prior to the onset of the thromboembolic events. The other six participants reported at least one and up to three risk factors for thromboembolism including a previous thromboembolic event, hypercholesterolaemia, diabetes mellitus and obesity. All participants received appropriate hospital care and were discharged without severe disability or impairment. An elderly male was diagnosed with new portal vein thrombosis and a resolving subclavian vein thrombosis, on ultrasound and CT imaging as an outpatient 19-days post vaccination. He also tested positive for COVID-19 two days later as part of admission investigations. He had no thrombocytopaenia and antibodies to platelet factor 4 were negative. He recovered after appropriate treatment. No cases of TTS were reported after receiving the second dose of Ad26.COV2.S.

Four immune system disorders were reported: two allergic reactions; one case of reactogenicity that required hospitalisation, and a flare of fibromyalgia. All four were reported by females, with a median age of 37 years (IQR: 25–51). Time to onset of the events were on the day of or one day post vaccination. One participant with fibromyalgia flare required hospitalisation on day 13 post vaccination, two cases with allergic reactions did not meet anaphylaxis criteria, and one participant with reactogenicity received antibiotic and steroid cover and was discharged when all investigations were normal except for mildly elevated inflammatory markers.

Neurological disorders included generalised seizures (n = 3), one case of aseptic meningitis and one case of GBS. All reported seizures were in individuals known with epilepsy and occurred within 12 h of vaccination. The case of GBS occurred in a 50-year-old female who reported pain in the neck radiating down to the left shoulder and upper limb 42 days after receiving the second dose of Ad26.COV2.S. Symptoms progressed with reports of subsequent difficulty swallowing and weakness of both lower limbs. Investigations including chest radiograph, electrocardiogram, blood specimens (full blood count, urea, creatinine and electrolytes, C-reactive protein, and cardiac markers) were all within normal limits. Seven days after the initial symptoms, the patient noted drooping of the left corner of her mouth, and weakness of her upper limbs. She was diagnosed with GBS and treated with intravenous immunoglobulins for 7 days, then transferred to a rehabilitation centre where she received care for a further 15 days. At the time of writing the participant had returned to work with minimal residual left upper and lower limb weakness.

The O/E analysis of thromboembolic and neurologic AESIs is summarised in Table 3. Amongst the thromboembolic disorders, pulmonary embolism had the highest O/E ratio of 0.23 (O/E 95 % CI 0.05–0.66). The O/E ratios of other thromboembolic disorders (cerebrovascular accidents, deep vein thrombosis and myocardial infarctions) were even lower, with narrow confidence intervals that did not include 1. The observed incidence of GBS is higher than the expected population incidence (O/E ratio of 2.02), however confidence intervals were wide and included 1.

Table 3. Observed versus expected (O/E) analysis[1] of Adverse Events of concern.

Adverse event	Observed count (WHO AEFI Causality Assessment Category)	Observed incidence rate per 100,000 PY	Expected count	Expected incidence rate per 100,000 PY	O/E ration (95 %CI)
Thromboembolic disorders					
Cerebrovascular accidents	2 (B2,C)	3.3	64.8	108,6	0.03 (0–0.11)
Pulmonary embolism	3 (B1,B1,C)	5.0	13.3	22.3	0.23 (0.05–0.66)
Deep vein thrombosis	1 (B1)	1.7	19.2	32.2	0.05 (0–0.29)
Myocardial Infarction	1 (B1)	3.3	134.9	226	0.01 (0–0.04)
Portal vein thrombosis	1 (B1)	1.7	0.4	0.7	2.39 (0.06–13.33)
Neurological disorders					
Guillain-Barré syndrome	1 (B1)	1.7	0.5	0.83	2.02 (0.05–1.25)
Seizure	3 (B1, B1, B1)	5.0	43.8	73.3	0.07 (0.01–0.20)

4. Discussion

The Sisonke 2 study administered a Ad26.COV2.S booster dose to 240,474 healthcare workers in South Africa who had received a first dose of Ad26.COV2.S as part of the Sisonke study. Analysis of this second vaccination administered 6–9 months after the first dose, showed a vaccine effectiveness of 85 % against COVID-19 hospitalisation [2], [17]. Here, we demonstrate in a large cohort with enhanced safety reporting and active monitoring that the second dose of Ad26.COV2.S was safe to administer and generally well tolerated.

Fewer adverse events were reported in those who received the second dose of Ad26.COV2.S (1.0 %) in comparison to the first dose (2.2 %) reported in the Sisonke study(1). This pattern is in keeping with reports of decreased reactogenicity after the second dose in the ChAdOx1-S and ENSEMBLE 2 trials, and different to reports on the mRNA platforms where solicited systemic AEs were noted to increase in severity and duration after the second dose. The proportion of SAEs at approximately 1.2 % was comparable to reports for viral vector and mRNA COVID-19 vaccines [18], [19].

The majority of safety events of concern, including TTS, thromboembolic events did either not occur or occurred less frequently than expected in a comparable unvaccinated population except for the case of portal vein thrombosis where COVID-19 infection and a probable underlying clotting disorder contributed to the aetiology [8], [10], [20]. There was a single

case of GBS, which remains a safety event of concern for viral vector COVID-19 vaccines [21], [22]. Causality assessment of serious adverse events per the WHO adverse event following immunisations were classified as B1: potential signal and maybe considered for investigation. Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event or C: coincidental underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine [23].

Our study had some limitations. First, most safety events were self-reported, which could have led to underreporting. However, we used an enhanced safety reporting system, that had already been tested in the Sisonke trial, and included several levels of reporting options by participants, research site staff, and healthcare providers. Second, for the O/E analysis, the comparator cohort data sources varied in follow up time and geographic location, as there are limited reliable comparator data for the South African healthcare worker population. Third, as TTS is a very rare AE our sample may not have had the statistical power to detect a rise in TTS, especially if TTS is less common after the second dose [24]. Finally, we excluded 43 Sisonke participants from receiving a homologous boost if they had experienced SAEs/AESIs after the first Ad26.COV2.S vaccination. While this could have been reduced the number of AEs, the number of exclusions were very small.

On 16 December 2021, the United States Advisory Committee on Immunization Practices recommended preferential use of mRNA COVID-19 vaccines over Ad26.COV2.S for people older than 18 years. This recommendation was based on the availability of alternative mRNA vaccines and the safety concern of rare events of TTS with the Ad26.COV2.S vaccine [20].

In keeping with the WHO recommendations for effective and safe use where heterologous schedules may not be available [9], the large-scale Sisonke 2 study demonstrates that an additional dose of Ad26.COV2.S can be safely administered to persons in whom the first dose was well tolerated and who are at lower risk of thromboembolic events. We provide evidence that the Ad26.COV2.S vaccine remains a valuable intervention if the supply of other vaccines is limited or where mRNA vaccine cold chain requirements cannot be maintained, especially in resource-limited settings.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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