Real-world effectiveness of Ad26.COV2.S or BNT162b2 booster vaccines against severe COVID-19 in adults who received a primary dose of Ad26.COV2.S in South Africa during the Delta period: A retrospective cohort study using medical scheme data

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Background. From March 2020 to June 2022, South Africa (SA) confronted successive waves of COVID-19, each linked to emerging SARS-CoV-2 variants. Vaccines played a critical role in preventing severe disease and death, but as new SARS-CoV-2 variants emerged, with increasing breakthrough infections, questions arose about the real-world effectiveness of first-generation vaccines containing the ancestral strain against evolving variants including Delta and Omicron BA.1 and BA.4/5 SARS-CoV-2.
Objectives. To assess the real-world effectiveness of ancestral strain booster doses (either Ad26.COV2.S or BNT162b2) in preventing severe COVID-19 outcomes, including hospitalisation, admission to critical care and death, among essential workers in SA who received a primary dose of Ad26.COV2.S against emerging SARS-CoV-2 variants.
Methods. A retrospective cohort study was conducted using data from a large private health insurance scheme. Individuals who received a single dose of Ad26.COV2.S as their primary vaccination were included. Time-varying Cox regression models were used to assess the effectiveness of boosting with either Ad26.COV2.S or BNT162b2 v. not boosting against severe COVID-19 outcomes associated with emerging variants, adjusting for various demographic and clinical factors.
Results. By August 2021, a total of 407 961 individuals received a first dose of Ad26.COV2.S, of whom 350 688 were eligible for and 332 286 included in the vaccine effectiveness (VE) analysis. Of these, 206 359 (62%) received no further doses, while 113 957 (34%) received a second dose of Ad26.COV2.S and 11 970 (4%) received a second dose of BNT162b2 by August 2022. During the follow-up period (November 2021 - August 2022), 1 125 COVID-19-related hospital admissions, 198 admissions to critical care and 41 COVID-19-related deaths were recorded. Adjusted relative VE against severe outcomes was 34% (95% confidence interval (CI) 19 - 45) for hospital admission, 51% (95% CI 22 - 70) for critical care admission, and 89% (95% CI 13 - 98) for COVID-19-related death.
Conclusion. While most participants remained unboosted, administration of either ancestral strain Ad26.COV2.S or BNT162b2 vaccination provided protection against severe COVID-19 outcomes among essential workers in SA during the dominance of the Omicron BA.1 and BA.4/5 variants, demonstrating cross-strain protection.

Keywords: COVID-19 vaccines, essential workers, real-world effectiveness, boosting, Ad26.COV2.S, BNT162b2

S Afr Med J 2025;115(7):e2532. https://doi.org/10.7196/SAMJ.2025.v115i7.2532

The first case of COVID-19 in South Africa (SA) was reported in March 2020, with the subsequent pandemic characterised by multiple waves that emerged subsequent to the initial ancestral strain wave, each associated with the emergence of a new SARS-CoV-2 strain – referred to as variants of concern. The first wave (June - August 2020) was associated with the ancestral strain (D614G), the second (November 2020 - January 2021) and third (May - September 2021) waves with the Beta and Delta strains, respectively, and the fourth (November 2021 - February 2022) and fifth (April - June 2022) waves with the Omicron strains (Fig. 1). Hospitalisations and deaths first uncoupled from infections during the first Omicron wave, attributed to hybrid immunity.[1-4]

The rapid development of efficacious vaccines against the ancestral strain was shown to be protective against symptomatic infection, severe illness, hospitalisation and death, prior to the emergence of new variants.[5] During the Beta wave, SA was unable to demonstrate efficacy of the ChAdOx1 vaccine,[6] but was able to show efficacy of the single-dose Ad26.COV2.S, prompting a rapid switch to the latter vaccine.[7] SA's vaccination programme then followed a globally unique path.The first phase comprised provision of investigational product single-dose Ad26.COV2.S to half a million health workers as part of the nationwide Sisonke phase 3B study in early 2021, before emergency use authorisation in the USA or SA occurred.[8] In total, 501 230 health workers received a first dose of Ad26.COV2.S before the Delta wave. Wider roll-out of BNT162b2 and Ad26.COV2.S followed emergency use vaccination approval, with older people first eligible for vaccination with BNT162b from May 2021 (Fig. 1). In June, a primary dose of Ad26.COV2.S was first extended to other essential workers, principally teachers, police and civil servants. Initial analysis of the Sisonke phase 3B study until mid-July 2021 (during the Beta and Delta waves) confirmed a high rate of vaccine effectiveness (VE) for the single-dose Ad26.COV2.S vaccine for all severe COVID-19 outcomes: 67% (95% confidence interval (CI) 62 - 71) against COVID-19-related hospitalisation, 75% (95% CI 69 - 82) against COVID-19-related hospital admission requiring critical or intensive care, and 83% (95% CI 75 - 89) against COVID-19-related death.[8]

In November 2021, before the Centers for Disease Control and Prevention (CDC) recommended switching to a two-dose primary regimen for Ad26.COV2.S,[9] and before any booster doses were available in SA, the South African Medical Research Council (SAMRC) offered and enrolled health workers who had participated in the Sisonke study a second dose of Ad26.COV2.S as part of the follow-up Sisonke 2 study. The emergence of variants of concern had resulted in growing disquiet about the effectiveness of vaccines developed against the SARS-CoV-2 ancestral strain, and already there were early signs that vaccine-induced immunity waned within months.[10,11] The ENSEMBLE2 study results had also been released, confirming additional protection and an acceptable safety profile of a second dose of Ad26.COV2.S provided 2 months after the primary dose.[12] In total, 240 488 health workers who received a primary dose of Ad26.COV2.S as part of the Sisonke 1 study received a second dose of Ad26.COV2.S as part of the Sisonke 2 study before the peak of the Omicron BA.1 wave. Second doses of Ad26.COV2.S were made widely available as part of the national vaccination programme from just before Christmas 2021 (Fig. 1).

Following a late 2021 CDC decision to preferentially recommend mRNA vaccines over Ad26.COV2.S, data on the effectiveness of

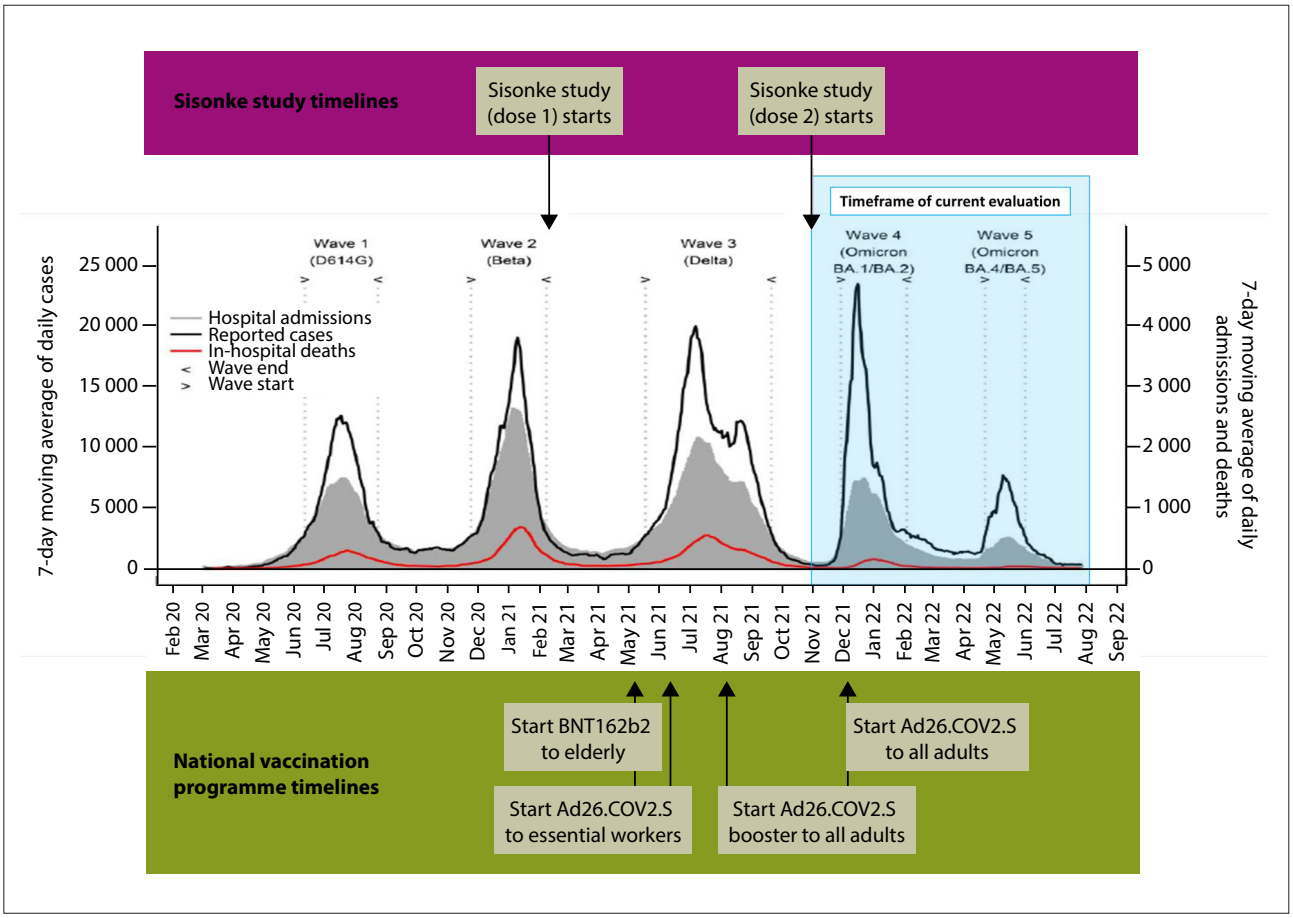

Fig. 1. COVID-19 waves in South Africa and key dates for the Sisonke study and the national vaccination programme.

boosters in people whose primary dose was Ad26.COV2.S are limited, and very few data from Africa have been published. We previously reported on early analysis of the effectiveness of a second dose of Ad26.COV2.S and found a high VE against hospital admission (72%; 95% CI 59 - 81) 1 - 2 months after the second dose was administered during the fourth (Omicron-associated) wave in SA.[13] The objective of the analysis reported in the present article was to evaluate the effectiveness of second doses (either BNT162b2 or Ad26.COV2.S) among essential workers who received a single dose of Ad26.COV2.S as their primary vaccination series for the full period during which the Omicron BA.1 and BA.4/5 variants were dominant (November 2021 - August 2022). We set out to include a comparison of homologous v. heterologous regimens, but the numbers of people who took up different boosters were too low to allow a meaningful analysis.

Methods

Data sources

We used data from a health insurance scheme that provided healthcare funding coverage for 757 222 principal members and their dependants across a range of sectors at the time. The data set included essential workers who received the Ad26.COV2.S vaccine as part of the Sisonke studies, and/or the mid-2021 campaign for other essential workers, and/or the general national vaccination programme. Data available from the scheme included claims data for COVID-19 vaccinations, hospitalisation records, and known comorbidities. The data set was enriched through linkage with SA's national vaccination database, which recorded all vaccinations including those provided as part of the Sisonke studies, and the National Population Register, which documents all deaths. Deterministic data linkage using SA civil identification numbers was used following completion of data sharing agreements. Linkage was conducted in secure environments, shared variables were deleted after linkage according to a prespecified standard operating procedure, and only anonymised data were analysed. We included all individuals who received a single dose of the Ad26.COV2.S vaccine as their primary vaccination, whether through the Sisonke studies or the national vaccination programme. Variable definitions and data sources are provided in Supplementary Table 1 (available online at http://coding.samedical.org/file/2347). We focused on severe disease (hospitalisations and deaths) as these data were most complete, after linkages. Reporting is compliant with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[14]

Statistical analysis

Time-varying Cox regression models were used to assess the effectiveness of boosting with either Ad26.COV2.S or BNT162b2 v. not boosting against severe COVID-19 outcomes associated with emerging variants, adjusting for various demographic and clinical factors. This statistical approach allowed us to estimate the effectiveness of boosting with either Ad26.COV2.S or BNT162b2 after a primary dose of Ad26.COV2.S v. not boosting against: (*i*) COVID-19-related hospitalisation; (*ii*) COVID-19-related hospitalisation requiring critical or intensive care; or (*iii*) COVID-19-related death, ≥14 days after the second dose during the Omicron BA.1 and BA.4/5 waves. Hospitalisations were considered to be COVID-19 related if the primary reason for admission was COVID-19 (ICD code U07.1) as submitted by the attending physician (Supplementary Table 1, http://coding.samedical.org/file/2347). In the case of COVID-19 hospitalisations requiring critical or intensive care, the date on which the individual was first admitted to hospital during the follow-up period was used, even if the person was later transferred to critical or intensive care. COVID-19 deaths were defined as deaths not known to be due to unnatural reasons (road traffic accidents, homicide, suicide), either during or within 3 months of a hospitalisation for COVID-19.

We evaluated members from 9 November 2021, when second doses of Ad26.COV2.S first became available to health workers through the Sisonke 2 study. In our model, booster status was treated as a time-varying exposure variable allowing for individual participants to contribute exposure time both before and after boosting. Those who did not receive a second dose only contributed to unboosted exposure time. Calendar time was used instead of a time-to-event scale. This approach is intuitive for analyses of vaccines for some infectious diseases, as risk and force of infection can vary substantially over time.[15,16]

For individuals who did not receive a booster, their 'unboosted' time at risk started from 9 November 2021 and ended at the earliest of occurrence of: (*i*) a study endpoint; (*ii*) the individual leaving the health insurance scheme; or (*iii*) the censor date of 31 August 2022, whichever came first. Among individuals who received boosters, time at risk during the unboosted period started from 9 November 2021 and ended at the earliest of occurrence of: (*i*) a study endpoint; (*ii*) receipt of a second dose; (*iii*) the individual leaving the health insurance scheme; or (*iv*) the censor date of 31 August 2022, whichever came first. Time at risk during the boosted period commenced 14 days after the receipt of the second dose and ended at the earliest of occurrence of: (*i*) a study endpoint; (*ii*) the individual leaving the health insurance scheme; or (*iii*) the censor date of 31 August 2022, whichever came first.

The following conditional variables were included in the multivariable model: age of the individual in the categories 18 - 39, 40 - 49, 50 - 59 and ≥60 years; sex; whether they were enrolled in a Sisonke study (yes/no); evidence of SARS-CoV-2 on or before 9 November 2021 (yes/no); presence or absence of the comorbidities HIV, hypertension, diabetes, chronic respiratory disease and cardiovascular disease; income band (lower income (<ZAR18 000 per month), low income (ZAR18 000 - 21 999 per month), middle income (ZAR22 000 - 27 999 per month), upper income (≥ZAR28 000 per month)); geographical location (province); and time between 9 November 2021 (the earliest date of a participant receiving the booster) and each participant's date for the primary dose (Supplementary Table 1, http://coding.samedical.org/file/2347). We performed separate analyses for each endpoint. VE was calculated as (1 – conditional hazard ratio) × 100, with 95% CIs. Analyses were performed using SAS (Statistical Analysis Software) version 9.4 (SAS Institute, USA) and Stata SE version 17 (StataCorp, USA) statistical software.

Ethical considerations

The Sisonke studies were approved by the South African Health Products Regulatory Authority (SAHPRA) and the health research ethics committees in the jurisdictions of which Sisonke clinical research sites were located: Pharma Ethics (ref. no. 211023480), the University of KwaZulu-Natal Biomedical Research Ethics Committee (ref. no. M21/10/007-COVID-19), the University of Cape Town Human Research Ethics Committee (ref. nos 00003531/2021 and 00003543/2021), the Sefako Makgatho University Research Ethics Committee (ref. no. SMUREC/M/289/2021:CR), the SAMRC Human Research Ethics Committee (ref. no. EC046-11/2021), and the University of the Witwatersrand Human Research Ethics Committee (ref. no. 211101). The study protocol and statistical analysis plan made provision for analyses inclusive of other essential workers who received vaccines as part

Table 1. Characteristics of individuals stratified by vaccination series received by the end of the study

Characteristic	1 dose Ad26.COV2.S (*n*=206 359), *n* (%)*	2 doses Ad26.COV2.S (*n*=113 957), *n* (%)*	Ad26.COV2.S + BNT162b2 (*n*=11 970), *n* (%)*	3 doses Ad26.COV2.S (*n*=10 855), *n* (%)*	3 doses combination: Ad26.COV2.S + BNT162b2 (*n*=7 547), *n* (%)*	All (*N*=350 688), *n* (%)*
Age (years), median (IQR)†	46 (38 - 53)	49 (41 - 55)	50 (43 - 55)	51 (44 - 56)	51 (43 - 56)	48 (39 - 54)
Age groups (years)†						
18 - 39	55 898 (27.1)	20 618 (18.1)	1 901 (15.9)	1 397 (12.9)	1 101 (14.6)	80 915 (23.1)
40 - 49	64 290 (31.2)	34 133 (30.0)	3 296 (27.5)	2 984 (27.5)	1 963 (26.0)	106 666 (30.4)
50 - 59	72 337 (35.1)	48 113 (42.2)	5 717 (47.8)	4 858 (44.8)	3 375 (44.7)	134 400 (38.3)
60 - 69	13 512 (6.5)	10 815 (9.5)	1 020 (8.5)	1 534 (14.1)	1 014 (13.4)	27 895 (8.0)
70 - 79	250 (0.1)	246 (0.2)	32 (0.3)	73 (0.7)	82 (1.1)	683 (0.2)
≥80	72 (<0.1)	32 (<0.1)	4 (<0.1)	9 (0.1)	12 (0.2)	129 (<0.1)
Sex						
Female	152 576 (73.9)	86 175 (75.6)	8 892 (74.3)	7 921 (73.0)	5 566 (73.8)	261 130 (74.5)
Male	53 783 (26.1)	27 782 (24.4)	3 078 (25.7)	2 934 (27.0)	1 981 (26.2)	89 558 (25.5)
Personal income band						
Lower (<ZAR18 000 per month)	48 133 (23.3)	20 554 (18.0)	2 348 (19.6)	1 687 (15.5)	1 121 (14.9)	73 843 (21.1)
Low (ZAR18 000 - 21 999 per month)	76 171 (36.9)	42 852 (37.6)	3 134 (26.2)	4 543 (41.9)	2 432 (32.2)	129 132 (36.8)
Middle (ZAR22 000 - 27 999 per month)	47 769 (23.1)	25 318 (22.2)	3 592 (30.0)	1 790 (16.5)	1 460 (19.3)	79 929 (22.8)
Upper (≥ZAR28 000 per month)	32 176 (15.6)	24 646 (21.6)	2 896 (24.2)	2 832 (26.1)	2 532 (33.5)	65 082 (18.6)
Unknown	2 110 (1.0)	587 (0.5)	0	3 (<0.1)	2 (<0.1)	2 702 (0.8)
Geographical location						
Eastern Cape	26 104 (12.6)	17 319 (15.2)	2 193 (18.3)	1 738 (16.0)	1 546 (20.5)	48 900 (13.9)
Free State	11 665 (5.7)	8 718 (7.7)	792 (6.6)	894 (8.2)	604 (8.0)	22 673 (6.5)
Gauteng	39 261 (19.0)	18 664 (16.4)	2 466 (20.6)	1 055 (9.7)	972 (12.9)	62 418 (17.8)
KwaZulu-Natal	53 713 (26.0)	22 863 (20.1)	2 706 (22.6)	1 576 (14.5)	1 481 (19.6)	82 339 (23.5)
Limpopo	25 650 (12.4)	15 236 (13.4)	1 272 (10.6)	2 172 (20.0)	626 (8.3)	44 956 (12.8)
Mpumalanga	16 222 (7.9)	7 512 (6.6)	475 (4.0)	718 (6.6)	188 (2.5)	25 115 (7.2)
North West	14 733 (7.1)	8 207 (7.2)	709 (5.9)	646 (6.0)	287 (3.8)	24 582 (7.0)
Northern Cape	4 112 (2.0)	2 587 (2.3)	277 (2.3)	311 (2.9)	184 (2.4)	7 471 (2.1)
Western Cape	14 890 (7.2)	12 849 (11.3)	1 080 (9.0)	1 745 (16.1)	1 658 (22.0)	32 222 (9.2)
Unknown	9 (<0.1)	2 (<0.1)	0	0	1 (<0.1)	12 (<0.1)
Clinical risk factors for severe COVID-19†						
Diabetes mellitus	18 132 (8.8)	12 915 (11.3)	1 578 (13.2)	1 605 (14.8)	1 070 (14.2)	35 300 (10.1)
Hypertension	43 762 (21.2)	29 602 (26.0)	3 450 (28.8)	3 208 (29.6)	2 310 (30.6)	82 332 (23.5)
HIV	39 452 (19.1)	19 582 (17.2)	2 154 (18.0)	1 574 (14.5)	973 (12.9)	63 735 (18.2)
Cardiovascular disease	2 426 (1.2)	1 821 (1.6)	219 (1.8)	203 (1.9)	171 (2.3)	4 840 (1.4)
Chronic renal disease	396 (0.2)	218 (0.2)	33 (0.3)	21 (0.2)	16 (0.2)	684 (0.2)
Chronic respiratory disease	5 920 (2.9)	4 139 (3.6)	531 (4.4)	474 (4.4)	421 (5.6)	11 485 (3.3)
Neurological disorders	1 705 (0.8)	1 019 (0.9)	133 (1.1)	98 (0.9)	81 (1.1)	3 036 (0.9)
Mental health disorders	12 308 (6.0)	7 745 (6.8)	1 043 (8.7)	881 (8.1)	766 (10.1)	22 743 (6.5)
Documented previous SARS-CoV-2 infection‡	18 299 (8.9)	9 615 (8.4)	1 253 (10.5)	873 (8.0)	727 (9.6)	30 767 (8.8)

*Except where otherwise indicated.

†Data as of 9 November 2021.

‡Data up to 3 months before 9 November 2021 (9 August - 9 November 2021).

of the national vaccination programme. The data extract was restricted to principal members of the medical insurance scheme who were essential workers, and who provided consent for their data to be used for research analyses at the time of enrolling in the scheme. The Sisonke 1 phase 3b study was registered at the South African National Clinical Trial Registry (DOH-27-022021-6844), ClinicalTrials.gov (NCT04838795), and the Pan African Clinical Trials Registry (PACTR202102855526180).

Results

Before the end of August 2022, 407 961 individuals belonging to a private health insurance scheme received a first dose of Ad26.COV2.S (Fig. 2). Of these, 126 642 (31%) received their first dose as part of the Sisonke study. We excluded 57 273 of the 407 961 individuals, 31 149 because they received their primary/first dose of Ad26.COV2.S ≤3 months before the study started in November 2021, and 20 187 because they received it afterwards, leaving 350 688

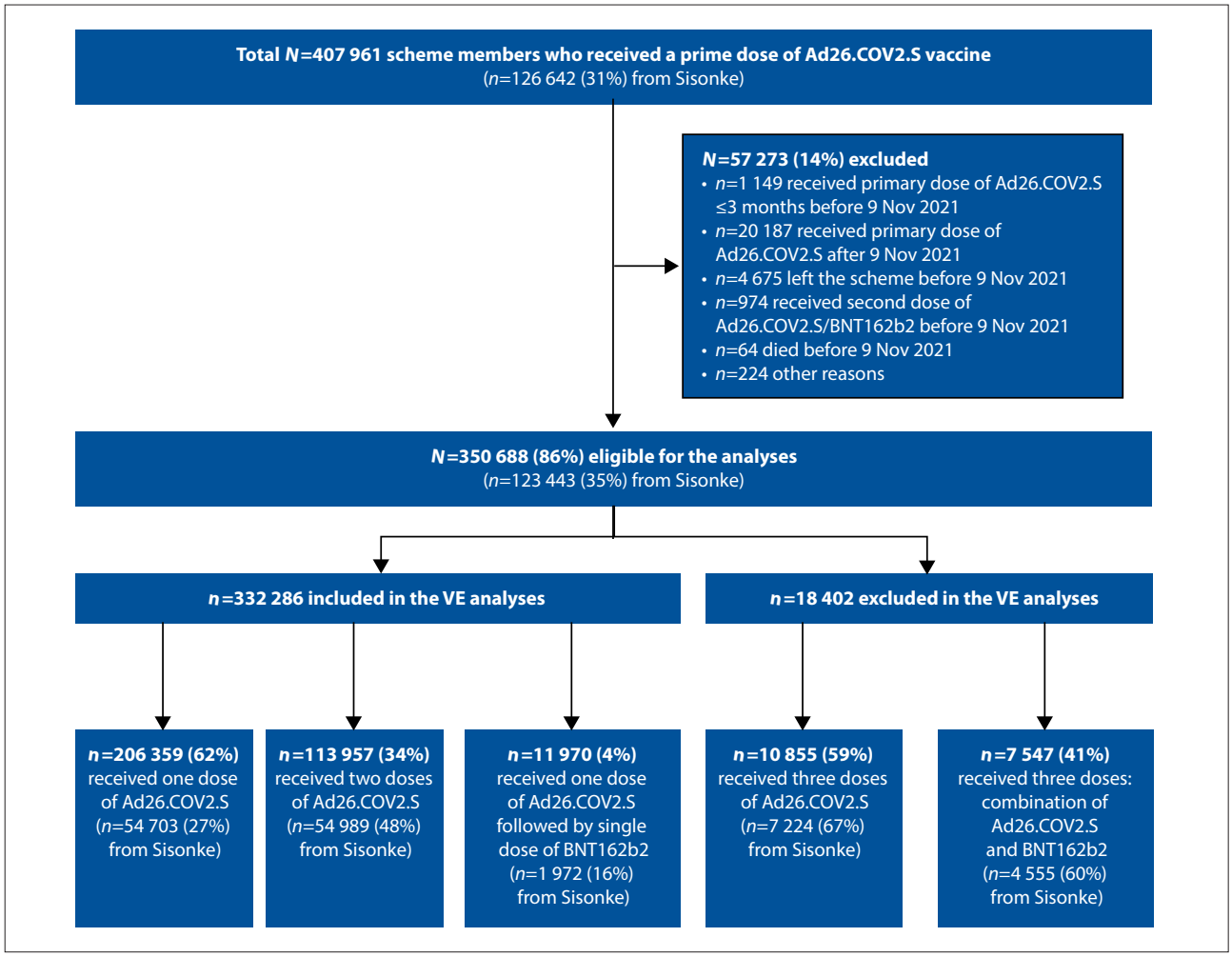

Fig. 2. Flow chart of the study population – individuals who received a primary dose of Ad26.COV2.S at least 3 months before second doses first became available (9 November 2021). (VE = vaccine effectiveness.)

individuals eligible and 332 286 contributing to the VE analysis. Of those included, 206 359 (62%) received no further doses of any vaccine by the end of follow-up, 113 957 (34%) received a second dose of Ad26.COV2.S, and 11 970 (4%) received a second dose of BNT162b2. Only 18 402 (5%) of eligible individuals received three doses of either vaccine with the third dose administered too close to the second dose with limited exposure time and therefore excluded in the VE analyses.

Almost three-quarters of the study population were women, with a median age (interquartile range (IQR)) of 48 (39 - 54) years (Table 1). Individuals who received two or more doses of vaccine tended to be older and to have a higher proportion of pre-existing non-communicable diseases (NCDs). Eighteen percent were living with HIV at the time of enrolment. Fewer than 10% had a documented SARS-CoV-2 infection during the 3 months before November 2021, which corresponded to the period between the Delta and Omicron BA.1 waves in SA. Individuals' geographical distribution by province mirrored the general population, although Gauteng Province was slightly under-represented and KwaZulu-Natal Province over-represented. Individuals who received their primary Ad26.COV2.S dose as part of the Sisonke study tended to be younger and to have a lower prevalence of NCDs (Supplementary Table 2, available online at http://coding.samedical.org/file/2348).

During the follow-up period, 1 125 hospital admissions for COVID-19 were recorded; 198 individuals required admission to critical or intensive care for COVID-19, and 41 died from COVID-19. The adjusted VE for two or more doses of vaccine compared with the single primary Ad26.COV2.S dose for COVID-19-related hospital admission was 34% (95% CI 19 - 45), for admission requiring critical or intensive care 51% (95% CI 22 - 70), and for COVID-19-related death 89% (95% CI 13 - 98) (Table 2 and Fig. 3). VE against hospital admission was lower among people aged ≥50 years compared with those aged 18 - 49 years (29% (95% CI 9 - 46) v. 38% (95% CI 16 - 55)), but did not differ between those with and without comorbidity risk factors for severe disease (Table 3). VE for people living with HIV was not different from that for people without HIV (37% (95% CI 3 - 59) v. 33% (95% CI 16 - 46)).

Discussion

We set out to evaluate the real-world effectiveness of a second dose of ancestral strain vaccine (Ad26.COV2.S or BNT162b2) in essential workers who had received a primary dose of Ad26.COV2.S. Overall, our results showed that in essential workers, mostly aged >45 years, who had received a primary dose of Ad26.COV2.S the administration of either booster vaccine protected against severe COVID-19 disease, including hospitalisation, admission to critical or intensive care and death, with VE of 34% (95% CI 19 - 45), 51% (95% CI 22 - 70) and 89% (95% CI 13 - 98), respectively. The effects of these ancestral strain vaccines were observed during the period in which Omicron BA.1 and BA.4/5 variants were dominant. The VE gradient observed

Table 2. Relative VE of any subsequent doses (Ad26.COV2.S or BNT162b2) compared with one primary dose of Ad26.COV2.S for severe COVID-19 outcomes

Outcome	VE (overall), % (95% CI)	VE (Sisonke recipients only), % (95% CI)	VE (other essential workers), % (95% CI)
Any hospital admission recorded as due to COVID-19	34 (19 - 45)	40 (23 - 53)	13 (–20 - 37)
Hospital admission requiring critical or intensive care	51 (22 - 70)	Not analysed	Not analysed
COVID-19-related death	89 (13 - 98)	Not analysed	Not analysed

VE = vaccine effectiveness; CI = confidence interval.

Table 3. Relative VE of any subsequent doses (Ad26.COV2.S or BNT162b2) compared with one primary dose of Ad26. COV2.S for all COVID-19 hospital admissions for age groups, HIV status and comorbidities

Outcome	VE (overall), % (95% CI)
Any hospital admission recorded as due to COVID-19 among those aged 18 - 49 years	38 (16 - 55)
Any hospital admission recorded as due to COVID-19 among those aged ≥50 years	29 (9 - 46)
Any hospital admission recorded as due to COVID-19 among those living with HIV	37 (3 - 59)
Any hospital admission recorded as due to COVID-19 among those living without HIV	33 (16 - 46)
Any hospital admission recorded as due to COVID-19 among those with a documented comorbidity	34 (7 - 53)
Any hospital admission recorded as due to COVID-19 among those without a documented comorbidity	30 (11 - 45)

VE = vaccine effectiveness; CI = confidence interval.

across hospitalisations, admissions to critical or intensive care and deaths was also reassuring and in keeping with vaccination offering most protection against severe outcomes. We were unable to compare heterologous with homologous boosting regimens in people whose primary series was a primary Ad26.COV2.S dose, because of the low number of people who took up heterologous boosting before the pandemic ended (Fig. 2). Overall, our findings are consistent with a test-negative case-control study that included 16 826 hospital admissions for acute respiratory infections among individuals from the same health insurance scheme, which showed a similar VE of 45% (95% CI 30 - 57) for boosters given to individuals who received a primary Ad26.COV2.S dose during the Omicron BA.4/5 period.[17]

A meta-analysis of 28 studies including >11 million individuals published before August 2022 showed VE against severe infection in the Omicron period following the primary series of 64% (95% CI 58 - 60) at 3 months, which fell to 49% (95% CI 36 - 64) within 6 months and was restored to 86% after the second or third booster dose.[18] However, only two of these studies were from low- and middle-income countries, the median (IQR) follow-up time for booster doses was relatively short at 16.5 (8.5 - 24) weeks, and only two studies reported VE for death.

Early immunogenicity data that suggested an enhanced response with mRNA boosting after a primary Ad26.COV2.S dose[19,20] seemed to follow through to real-world studies which demonstrated that heterologous boosting was more effective than homologous boosting, and that any boosting was better than none.[21-24] In our study, only 5.6% of the 350 688 individuals received heterologous boosters (as part of two or three total doses received) and there were too few outcome events to perform meaningful comparisons between homologous and heterologous boosting strategies.

Importantly, a critical observation from our study is that 59% of individuals received only one dose of Ad26.COV2.S before the end of the pandemic. Individuals not vaccinated through the Sisonke studies would only have become eligible for boosters several weeks into the Omicron wave, by which time the reduction in severity of illness caused by hybrid immunity was already in play.[4] While relative effectiveness of COVID-19 vaccines and boosters has been widely reported and many studies on intention to vaccinate have been published, less is known about predictors of actual COVID-19 vaccination uptake. A limited review from high-income countries found that vaccination uptake was higher among white individuals compared with black individuals, with lack of trust in governments, reduced perception of the risks of COVID-19, concerns about vaccine safety, and religious beliefs reported as barriers to uptake.[25] A longitudinal population-based survey from Hong Kong also highlighted lack of trust in governments and showed that knowing someone who was already vaccinated was associated with an eight-fold odds of vaccine uptake.[26] A similar survey from SA confirmed that that awareness of others in the area being vaccinated and having a household member vaccinated predicted uptake and highlighted the potential of social proof interventions.[27] Nonetheless, predictors of vaccination uptake remain an under-reported dimension of effectiveness evaluations using administrative data, and would be important to understand before the onset of the next pandemic.

If such a high proportion of people only take up one dose of vaccine, the choice of that first vaccine is critical. While the levels of immediate protection provided by mRNA vaccines were impressively high and associated with steep rises in antibody titres, their protection waned rapidly. In contrast, the vector-based vaccines (such as Ad26.COV2.S) were associated with lower initial levels of antibodies but greater cellular immunity, which is more important for durable responses against severe disease.[28] However, data on immunogenicity, efficacy and effectiveness must be considered against the realities of a pandemic response, with inequitable access to different vaccines, differing cold-chain requirements, and individual and social behaviours ultimately determining their potential to reduce the burden of morbidity and mortality.

The provision of booster doses to Sisonke participants coincided with the start of the Omicron wave. Cases were rising at an unprecedented rate and the relative severity of associated COVID-19 had yet to be established, but debate regarding choice of booster vaccine was robust.[29] Initial immunogenicity data suggested greater response with heterologous boosting, and some health workers were more disposed towards BNT162b2 following higher VE of the two-dose primary series against severe disease compared with single-dose Ad26.COV2.S. Only half of the eligible health workers elected to take up the second Ad26.COV2.S dose during the Sisonke 2 study. It was mid-March 2022 before the SAHPRA approved BNT162b2 boosters, by which time the fourth wave was essentially over. Similarly, the Sisonke 1 study had provided first doses of Ad26.COV2.S ahead of the Delta wave and before BNT162b2 was available in SA. This is

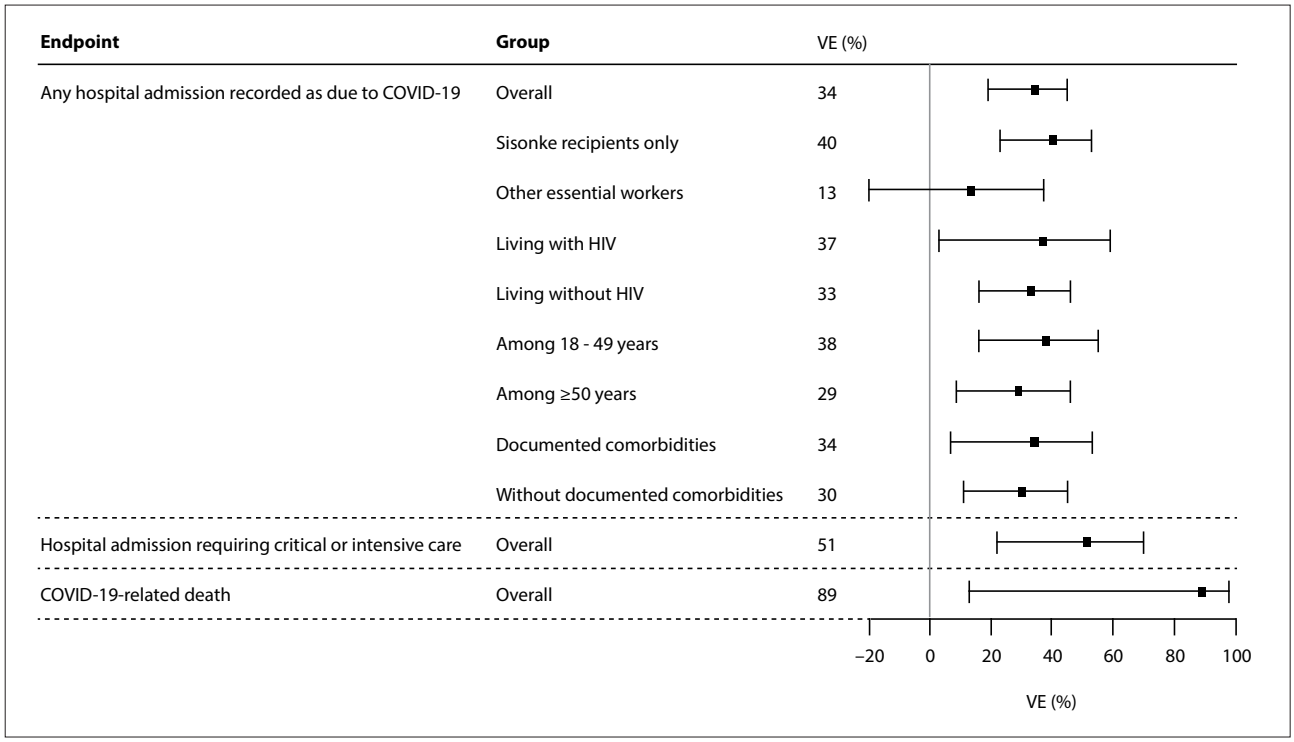

Fig. 3. Forest plot showing relative vaccine effectiveness of any subsequent doses (Ad26.COV2.S or BNT162b2) compared with one primary dose of Ad26.COV2.S. (VE = vaccine effectiveness.)

perhaps the greatest learning from the Sisonke experience – that in pandemic circumstances days matter, and that ultimately the best vaccine is the one in your arm.

Strengths of the study include the large number of individuals included in the analysis, the use of statistical methods that allowed inclusion of all individuals' at-risk time before and after administration of the second dose, the duration of follow-up which extends the full duration of the pandemic, the linkage to the National Population Register and reporting of death as an outcome, and the data set that fairly mirrored SA's socioeconomically diverse population. Nonetheless, differences in outcomes between insured and uninsured populations are likely, and treatment of COVID-19 in the private sector has been associated with better outcomes.[30] Although it is difficult to know whether this would positively or negatively influence effectiveness of booster doses, caution should be exercised when generalising to the wider SA population. Other limitations include the inability to compare subgroups of interest because of low uptake (e.g. homologous v. heterologous boosting), dependence on admitting clinicians to report COVID-19 as the reason for admission, and possible misclassification owing to incomplete vaccination and/or admission data inherent in all administrative data sets.

Conclusion

Subsequent doses of the ancestral strain versions of the Ad26.COV2.S or BNT162b2 vaccines conferred protection against severe COVID-19 outcomes, including hospitalisation and death, in people whose first vaccination was a single dose of Ad26.COV2.S vaccine during the Omicron period and despite uncoupling of hospitalisation and death from infection. Early access of health workers and other essential workers to the Ad26.COV2.S vaccine provided timely and effective protection. The Sisonke experience remains globally unique in leveraging research to provide half a million health workers with first doses of vaccine ahead of the third wave and booster doses to close to half that number before the Omicron waves in a country and continent faced with inequitable and slow access to vaccines. Our analysis highlights the importance of timely access to vaccines during outbreaks as Africa faces ongoing emerging infectious diseases outbreaks such as mpox.[31]

Data availability. None.

Declaration. None.

Acknowledgements. We thank the healthcare workers who participated in the Sisonke study. We thank the clinical research site investigators, the study staff and teams, and the support staff at the SAMRC. We thank the research and data analytical teams at Medscheme and the private health insurance scheme. In particular, we thank Steven Dorfman and Stanley Moloabi. We also thank Paul Stoffels, Johan van Hoof and Abeda Williams from Janssen (Johnson & Johnson), who facilitated and provided the investigational product for Sisonke 1 and sponsored the doses for Sisonke 2. We thank the President of South Africa, Cyril Ramaphosa, and the previous Minister of Health, Zweli Mkhize, for their support. We thank Sandile Buthelezi, Anban Pillay, Lesley Bamford, Gaurang Tanna, Khadija Jamaloodien and the National Department of Health, and the nine provincial Departments of Health, vaccination sites and staff. We are also grateful for the support of the private medical clinics for partnering with Sisonke and establishing vaccination sites. We thank the Biovac Institute for vaccine storage and packing, Biocair South Africa and Leonard Lazarus for the distribution of the vaccines, and the National Joint Operational Intelligence Structure for ensuring safe deployment. We also thank Zameer Brey, Koleka Mlisana, Rob Botha, Penny Moore, Peter Gilbert and Holly Janes. We also thank the SAMRC for their unfailing support. We also thank the Hutchinson Cancer Research Institute of South Africa and Knowledge Translation Unit of the Health Foundation of South Africa staff for their hard work in providing training and oversight

of study operations. We thank Right to Care for their expansion in the rural areas of the Northern Cape and Eastern Cape provinces with the assistance of Josef Tayag and Thomas Minior, United States Agency for International Development (grant number AID-OAA-A-15-00070). We also thank our regulator, the SAHPRA, and the health research ethics committees who provided guidance and oversight. The content is solely the responsibility of the authors and does not necessarily represent the official views of Johnson & Johnson or our funders. The funders had an opportunity to review a preliminary version of the manuscript; however, the authors are solely responsible for the final content and interpretation.

Author contributions. GEG, L-GB, NG, AG, TR, NY-Z and LF contributed to conceptualisation and study design. LF, GEG, L-GB, SB, NF, SM, MS and IS contributed to the data governance and sharing agreements, data linkage and extraction of the data set on which the analysis was based. NY-Z and TR had access to the data and completed the analysis under the guidance of LF, GEG, L-GB, NG and AG. LF, NY-Z and TR wrote the first draft of the manuscript, and all authors contributed to and approved the final version. Funding was acquired by GEG.

Funding. Direct funding for the Sisonke study was provided by the National Treasury of South Africa, the National Department of Health, Solidarity Response Fund NPC, the Michael & Susan Dell Foundation, the Elma Vaccines & Immunisation Foundation (grant no. 21-V0001), and the Bill & Melinda Gates Foundation (grant no. INV-030342).

Conflicts of interest. L-GB declares honoraria for advisory roles from MSD, ViiV Health Care, and Gilead. All other authors declare no competing interests.

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Received 3 September 2024; accepted 16 April 2025.