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Estimation of vaccine effectiveness against SARS-CoV-2-associated hospitalization using sentinel surveillance in South Africa

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Abstract

Background: COVID-19 vaccine effectiveness (VE) studies leveraging systematic surveillance in sub-Saharan Africa are limited. We assessed the effectiveness of two vaccines (Pfizer BNT162b2 and Johnson & Johnson Ad26.COV2.S) against SARS-CoV-2-associated hospitalization in South African adults aged ≥18 years.

Methods: We conducted a test-negative case-control study using pneumonia surveillance data in South Africa. Inpatients with physician-diagnosed lower respiratory tract infection or suspected COVID-19, testing SARS-CoV-2 positive or negative from June 2021–March 2022, were cases or controls, respectively. Fully vaccinated individuals received one Ad26.COV2.S dose or two BNT162b2 doses ≥14-days before enrollment. VE was estimated using multivariable logistic regression for Delta- and Omicron BA.1/BA.2-predominant periods, stratified by age and HIV status.

Results: The study included 925 cases and 1890 controls; 38 (4%) cases and 186 (10%) controls were fully vaccinated with BNT162b2, and 30 (3%) cases and 94 (5%) controls with Ad26.COV2.S. The vaccine effectiveness of BNT162b2 against SARS-CoV-2-associated hospitalization over Delta and Omicron BA.1/BA.2 periods was 91% (95% CI: 52%, 98%) and 33% (-16%, 86%), respectively. The vaccine effectiveness of Ad26.COV2.S against hospitalization over Delta and Omicron BA.1/BA.2 periods was 72% (-36% ,94%), and -19% (-130%, 39%), respectively. The vaccine effectiveness of BNT162b2 against hospitalization over the Delta period was 94% (50%, 99%) and 89% (27%, 98%) among adults aged ≥60 years and HIV-uninfected, respectively.

Conclusions: The BNT162b2 vaccine was effective against SARS-CoV-2-associated hospitalization during the Delta period for adults aged ≥18 years, ≥60 years and those HIV-uninfected. VE for Ad26.COV2.S was inconclusive, potentially due to limited sample size or residual confounding. These findings highlight the utility of sentinel surveillance for estimating VE.

Keywords: SARS-CoV-2, sentinel surveillance, vaccine effectiveness, COVID-19, test-negative case control.

Introduction

By 2 April 2022, Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), accounted for more than 3 700 000 cases and 100 000 deaths in South Africa.[1,2] At the time of this study, South Africa had experienced four SARS-CoV-2 epidemic waves, dominated by the ancestral strain, Beta, Delta and Omicron BA.1/BA.2 variants, respectively.

The BNT162b2 mRNA (Pfizer) vaccine was approved for use in South Africa in May 2021, and the Ad26.COV2.S adenoviral vector (Johnson & Johnson) vaccine in February 2021.[3–6] The South African vaccination roll-out started in February 2021, prioritizing front-line and health care workers, followed by different age groups (starting with ≥60 years) and those with high-exposure occupations, and concluding with adults aged 18–34 years before the Delta

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variant wave dissipated. Further detailed recommendations are included in the Supplementary data (available at *IJE* online). As of 3 April 2022, 49% of the South African adult population had received a dose of the Ad26.COV2.S vaccine or at least one dose of the BNT162b2 vaccine.[6] Vaccine coverage by age group in April 2022 was 37% for those aged 18–34 years, 53% for those aged 35–49 years, 64% for those aged 50–59 years and 66% for those aged ≥60 years.[6]

Multi-site, randomized controlled trials (RCT) of vaccine efficacy estimated 95% efficacy against severe COVID-19 for the BNT162b2 vaccine and >65% against moderate to critical COVID-19 for the Ad26.COV2.S vaccine.[7,8] Since these studies, there have been multiple epidemic waves worldwide, each dominated by different SARS-CoV-2 variants that reacted differently to immune responses elicited by vaccines or previous infections.[9–11] Real-world estimates of the effectiveness of COVID-19 vaccines in resource-limited settings, particularly from sub-Saharan Africa (SSA), are limited.[12–15] Furthermore, despite studies reporting that people living with HIV (PLHIV) and those aged 60 years and above are at a higher risk for severe disease and death from SARS-CoV-2 infection, there are limited studies in SSA on the effectiveness of COVID-19 vaccines in these high-risk groups.[16–18] Ongoing emergence of new variants, updated vaccines and waning immunity will necessitate regularly updated vaccine effectiveness (VE) estimates for the foreseeable future. As countries move away from policies advocating universal testing for SARS-CoV-2 among hospitalized individuals, there is a need for systematic platforms for assessment of VE, similar to those used for influenza.[19,20] We aimed to describe real-world effectiveness of the BNT162b2 and Ad26.COV2.S SARS-CoV-2 vaccines against SARS-CoV-2-associated hospitalization in adults aged ≥18 years in South Africa, using data from national sentinel surveillance for pneumonia.

Methods

Surveillance programme

Following the first SARS-CoV-2 case in South Africa on 5 March 2020, the active pneumonia sentinel surveillance programme, established in 2009 for influenza virus and other respiratory pathogens, was expanded to incorporate SARS-CoV-2 molecular testing and sequencing. To enhance vaccine effectiveness (VE) estimation, three public hospitals were added to the existing seven, totalling 10 hospitals across six provinces. All medical admissions at surveillance hospitals from Monday through Friday were screened to see if they met the surveillance case definition. The programme enrolled consenting hospitalized patients or inpatients who met the case definition of a physician-diagnosed lower respiratory tract illness (LRTI) (e.g. bronchiolitis, pneumonia, bronchitis, and pleural effusion) or suspected COVID-19. Enrolled inpatients provided demographic and clinical data. COVID-19 vaccination status information was sourced from vaccination cards, hospital vaccine registers or the South African COVID-19 Electronic Vaccination Data System (EVDS) when available; if unavailable, then undocumented personal accounts were used. HIV status was collected from hospital files or pre-test counselling and testing, and previous SARS-CoV-2 infections were self-reported. Surveillance officers also collected nasopharyngeal swabs from all enrolled inpatients, placing them in universal transport medium stored at 4–8°C and transported to the National Institute for Communicable Diseases (NICD) within 72 h. Enrolled inpatients were followed until their discharge, transfer, or death.

Study design

We conducted a test-negative case-control (TND) study within South Africa's pneumonia sentinel surveillance programme from 28 June 2021 to 31 March 2022, aiming to estimate the vaccine effectiveness (VE) of BNT162b2 and Ad26.COV2.S. Participants, including cases and controls, were selected from this programme. The inclusion criteria were that participants should be: adults aged ≥18 years; who fulfilled the above mentioned surveillance case definition; had complete SARS-CoV-2 real-time reverse transcription polymerase chain reaction (rRT-PCR) results and vaccination records; and were eligible to receive SARS-CoV-2 vaccines under the South African vaccination roll-out plan at their time of enrolment. It should be noted that vaccination status was determined at enrollment and SARS-CoV-2 results were established after enrollment. Details of the vaccination plan and comprehensive programme methodologies are available in the Supplementary materials (available at *IJE* online) and prior publications.[17,21–24]

Laboratory procedures

Nucleic acids were obtained from a 200-µl sample of transport medium using an automated extraction system called MagNA Pure 96, along with the MP96 DNA and Viral NA Small Volume v2.0 extraction kit (Roche Diagnostics, Mannheim, Germany). These extracted nucleic acids were then subjected to rRT-PCR to detect the presence of SARS-CoV-2. Furthermore, for samples that tested positive for SARS-CoV-2, an additional analysis was conducted using variant PCR and/or sequencing at the NICD to determine the specific lineage or clade of the virus.[25] Further details about the rRT-PCR testing and sequencing methods are described in the Supplementary materials (available at *IJE* online).

Definition of cases, controls and variables

Cases and controls were selected from the surveillance programme from 28 June 2021 to 31 March 2022. Cases were enrolled inpatients who met the inclusion criteria and tested positive for SARS-CoV-2 by rRT-PCR, and controls were those who tested negative. Self-reported and/or documented COVID-19 vaccination status was categorized as fully vaccinated (one or more doses of Ad26.COV2.S or two doses of BNT162b2, administered at least 14 days prior to symptom onset), partially vaccinated (any vaccination not meeting the fully vaccinated criteria), or not vaccinated (no dose received). Inpatients with mixed vaccine types ($N=3$) or booster doses ($N=2$) were excluded. Time since vaccination was categorized into five group based on the number of days from the last vaccine dose to symptom onset: not vaccinated, partially vaccinated, 14–60 days, 61–120 days and >120 days following full vaccination.

Covariables, identified within the surveillance programme and known to influence vaccine effectiveness, included age group (18–34, 35–49, 50–59, ≥60 years), sex (male, female), race (Black, non-Black, unspecified), month of admission, previous self-reported SARS-CoV-2 infection (yes, no), HIV status (HIV uninfected, PLHIV and unknown), presence of at least one underlying condition (yes, no) and province.[26] The underlying conditions included are defined in the Table 1 footnote and in the Supplementary data (available at *IJE*

Table 1. Characteristics of hospitalized adults aged ≥18 years eligible for SARS-CoV-2 vaccination, who tested positive (cases) and negative (controls) for SARS-CoV-2 at 10 pneumonia surveillance sentinel hospitals in South Africa, 28 June 2021 to 31 March 2022

	Total ($N = 2815$) *n* (%)	Cases ($N = 925$) *n* (%)	Controls ($N = 1890$) *n* (%)	*P*-value
Age groups (years)				
18–34	515 (18)	139 (15)	376 (20)	<0.001
35–49	742 (26)	180 (19)	562 (30)	
50–59	566 (20)	212 (23)	354 (19)	
≥60	992 (35)	394 (43)	598 (32)	
Sex				
Male	1242 (44)	352 (38)	890 (47)	<0.001
Female	1573 (56)	573 (62)	1000 (53)	
Race				
Black	2302 (82)	719 (78)	1583 (84)	<0.001
Non-Black	511 (18)	205 (22)	306 (16)	
Unspecified	2 (0)	1 (0)	1 (0)	
Overall vaccination status[a]				
Not vaccinated	2235 (79)	765 (83)	1470 (78)	<0.001
BNT162b2 partially vaccinated	210 (7)	87 (9)	123 (7)	
Ad26.COV2.S partially vaccinated	22 (1)	5 (1)	17 (1)	
BNT162b2 fully vaccinated	224 (8)	38 (4)	186 (10)	
Ad26.COV2.S fully vaccinated	124 (4)	30 (3)	94 (5)	
HIV status				
Uninfected	1611 (57)	625 (68)	986 (52)	<0.001
Unknown	170 (6)	52 (6)	118 (6)	
PLHIV	1034 (37)	248 (27)	786 (42)	
PLHIV ($N = 1034$; $N = 248$; N = 86)				
CD4+ >200 cell/mm^3 or VL ≤10 000 copies/mL	513 (50)	136 (55)	377 (48)	0.037
CD4+ ≤200 cell/mm^3 or VL >10 000 copies/mL	313 (30)	59 (24)	254 (32)	
CD4+ missing and VL missing	208 (20)	53 (21)	155 (20)	
Previous self-reported SARS-CoV-2 infection				
No	1239 (44)	347 (38)	892 (47)	<0.001
Yes	62 (2)	15 (2)	47 (2)	
Unknown	1514 (54)	563 (61)	951 (50)	
Underlying condition[b]				
No	1201 (43)	387 (42)	814 (43)	0.535
Yes	1614 (57)	538 (58)	1076 (57)	
Enrolment period				
Delta-predominant	1728 (61)	627 (68)	1101 (58)	<0.001
Omicron BA.1/BA.2-predominant	1087 (39)	298 (32)	789 (42)	
Province				
Gauteng	809 (29)	199 (22)	610 (32)	<0.001
KwaZulu-Natal	643 (23)	249 (27)	394 (21)	
Mpumalanga	461 (16)	113 (12)	348 (18)	
North West	407 (14)	165 (18)	242 (13)	
Western Cape	495 (18)	199 (22)	296 (16)	

VL, viral load; HIV, human immunodeficiency virus; PLHIV, people living with HIV.

[a] Included cirrhosis of the liver, valvular heart disease, organ transplant, splenectomy, immunoglobulin, nephrotic disease, cerebral palsy, obesity, malignancy, other chronic lung diseases, chronic renal failure, coronary artery disease, any immunosuppressive condition, diabetes, autoimmune disease, spinal cord injury, other congenital disorder, chronic obstructive pulmonary disease (COPD)/emphysema, stroke, heart failure, sinusitis, sickle cell disease, burns, malnutrition, seizure disorder, prematurity, congenital heart disease, asthma, hypertension, currently pregnant, previous tuberculosis (TB) infection and current TB infection.

[b] Vaccination status defined as either fully vaccinated (receiving at least one dose of the Ad26.COV2.S vaccine or a second dose of the BNT162b2 vaccine ≥14 days before the symptom onset date), partially vaccinated (receiving any vaccine dose but not meeting the criteria to be classified as fully vaccinated) or not vaccinated (receiving no vaccine dose). The BNT162b2 vaccine is an mRNA COVID-19 vaccine manufactured by Pfizer-BioNTech, and the Ad26.COV2.S vaccine is a viral vector COVID-19 vaccine manufactured by Johnson & Johnson.

online). PLHIV were further categorized based on their immunosuppression level, using CD4+ count and viral load as markers: no severe immunosuppression (CD4+ count >200 cell/mm^3 or viral load ≤10 000 copies/mL), severe immunosuppression (CD4+ count ≤200 cell/mm^3 or viral load >10 000 copies/mL) and missing immunosuppression information (missing CD4+ count and viral load).

Variants and epidemic wave periods

Positive SARS-CoV-2 specimens were categorized into clades or lineages based on sequencing or variant PCR data: ancestral, Alpha, Beta, Delta, 20D(C.1.2), Omicron BA.1/BA.2 or unable to assign.[17] Positive specimens with missing sequencing results from a single dataset were imputed to the most prevalent variant during the collection period ($N = 89$). Epidemic wave periods were determined based on the proportion of a specific variant of concern in over 50% of available non-imputed sequenced specimens within the surveillance network in a week. The study period included two epidemic waves: the Delta-predominant period (2021 weeks 26–46, corresponding to 28 June—21 November 2021), and Omicron BA.1/BA.2-predominant period (2021 week 47–2022 week 13, corresponding to 22 November 2021–31 March 2022).

Sample size

With a significance level (α) of 0.05, precision of 10% and power of 80%, the minimum sample size required was 471 cases and 1884 controls for vaccine coverage of 40% and VE of 85%.[27]

Statistical analysis

Patient characteristics for cases and controls were described and compared using the chi square test. Multivariable logistic regression was used to estimate BNT162b2 and Ad26.COV2.S VE against SARS-CoV-2-associated hospitalization during the Delta-predominant period, the Omicron BA.1/BA.2-predominant period and the entire surveillance period of May 2021–March 2022. Multivariable logistic regression was also used to evaluate the BNT162b2 VE against SARS-CoV-2-associated hospitalization stratified by HIV status during these periods. Potential confounders that were adjusted for in the multiple logistic regression models included age group, sex, race, month of admission and province.[26] Propensity scores were performed yielding similar results with the logistic regression for sufficient sample sizes (Supplementary Table S4, available as Supplementary data at *IJE* online). VE was estimated as a percentage derived from the formula $(1 - odds\ ratio) \times 100\%$, where the odds ratio (OR) was obtained from the multivariable logistic regression models. Although partially vaccinated individuals were included in the models, their VE estimates were not reported due to small numbers, nor for any subgroups where the number of cases was zero. A *P*-value <0.05 was considered indicative of a potentially meaningful difference of VE estimate. Stata version 17 (StataCorp, College Station, TX) was used for analysis.

Results

Characteristics of cases and controls

Out of 2815 inpatients included, 925 (33%) cases were SARS-CoV-2-positive and 1890 (67%) controls were negative, with a predominance of individuals ≥60 years, females and those enrolled during the Delta-predominant period (Supplementary Figure S1, available as Supplementary data at *IJE* online; Table 1). PLHIV accounted for 27% (248/925) of cases and 42% (786/1890) of controls, with at most 32% immunosuppression noted in either subgroup.

Vaccination coverage was confirmed at 21% (580/2815), predominantly through self-reporting, with a subset validated by vaccination cards (23%, 134/580) and registry checks (12%, 71/580). Of the 580 vaccinated individuals, 39% received BNT162b2 and 21% Ad26.COV2.S fully, and 40% were partially vaccinated (Supplementary Figure S1, available as Supplementary data at *IJE* online). Among vaccinated cases, 43% (68/160) were fully vaccinated; of these, 56% received BNT162b2 and 44% received Ad26.COV2.S. For the vaccinated controls, 67% (280/420) were fully vaccinated, predominantly with BNT162b2 (66%) (Supplementary Figure S1, available as Supplementary data at *IJE* online). Notably, there were meaningful differences between cases and controls across multiple demographic and clinical variables (Table 1).

SARS-CoV-2 variant trends

Of 925 cases available for variant characterization throughout the study, 4 (0.4%) were ancestral strain, 1 (0.1%) Alpha, 3 (0.3%) Beta, 454 (49.1%) Delta, 7 (0.8%) 20 (DC.1.2) and 231 (25.0%) Omicron BA.1/BA.2; 225 (24.3%) could not be assigned to a variant because of low viral load (Figure 1).

BNT162b2 and Ad26.COV2.S VE estimates and by time since vaccination

BNT162b2 VE against SARS-CoV-2-associated hospitalization, after adjusting for confounders, was 51% [95% confidence interval (CI): 23%, 68%] overall. During the Delta- and Omicron BA.1/BA.2-predominant periods, VE was 91% (95% CI: 52%, 98%) and 33% (95% CI: -16%, 62%), respectively (Table 2). For inpatients aged ≥60 years, adjusted BNT162b2 VE reached 62% (95% CI: 27%, 80%) overall, with an increase to 94% (95% CI: 50%, 99%) during the Delta period, and a decrease to 54% (95% CI: -8%, 80%) during the Omicron BA.1/BA.2 period (Table 2). In HIV-uninfected inpatients, adjusted BNT162b2 VE was 67% (95% CI: 40%, 82%) overall and 89% (95% CI: 27%, 98%) during the Delta period (Table 2). Small sample sizes precluded VE estimation of BNT162b2 in PLHIV during variant-predominant periods (Table 2; and Supplementary Table S5, available as Supplementary data at *IJE* online). For fully vaccinated individuals, BNT162b2 VE was 74% (95% CI: 40%, 89%) overall and 89% (95% CI: 41%, 98%) in the Delta period within 14–60 days post-vaccination. BNT162b2 VE beyond 60 days post-vaccination and during the Omicron period were inconclusive (Table 2).

Ad26.COV2.S VE estimates and by time since vaccination

Ad26.COV2.S VE was -9% (95% CI: -83%, 35%), 72% (95% CI: -36%, 94%) and -19% (95% CI: -130%, 39%) during the entire, Delta- and Omicron BA.1/BA.2-predominant periods, respectively (Table 3). Ad26.COV2.S VE in inpatients aged ≥60 years was 16% (95% CI: -162%, 73%) overall, 31% (95% CI: -331%, 89%) during Delta and 10% (95% CI: -370%, 83%) during Omicron BA.1/BA.2 (Table 3). VE estimation of Ad26.COV2.S stratified by HIV status during variant-predominant periods and by time since vaccination was inconclusive (Table 3; and Supplementary Table S6, available as Supplementary data at *IJE* online).

Discussion

In this test-negative case-control analysis of national pneumonia surveillance data, we evaluated BNT162b2 and Ad26.COV2.S VE against SARS-CoV-2-associated hospitalization in South Africa. Our findings showed that two BNT162b2 doses were effective in preventing SARS-CoV-2-associated hospitalization in adult inpatients, including those aged ≥60 years, and HIV-uninfected participants during both the entire and the Delta-predominant periods. Protection was also observed in the 14–60 days post-BNT162b2 vaccination window, although effectiveness diminished over time.

The BNT162b2 VE estimates during the Delta period (91%) and within 14–60 days post-vaccination (89%) were consistent with previous reports from South Africa using private medical insurance data between 17 May and 23 September 2021 (92% and 94%, respectively) and other countries: Thailand (88%), Japan (>86%), Israel (97%, and the USA (90%) after the second dose.[15,28–31] These findings align with data demonstrating the Delta variant's

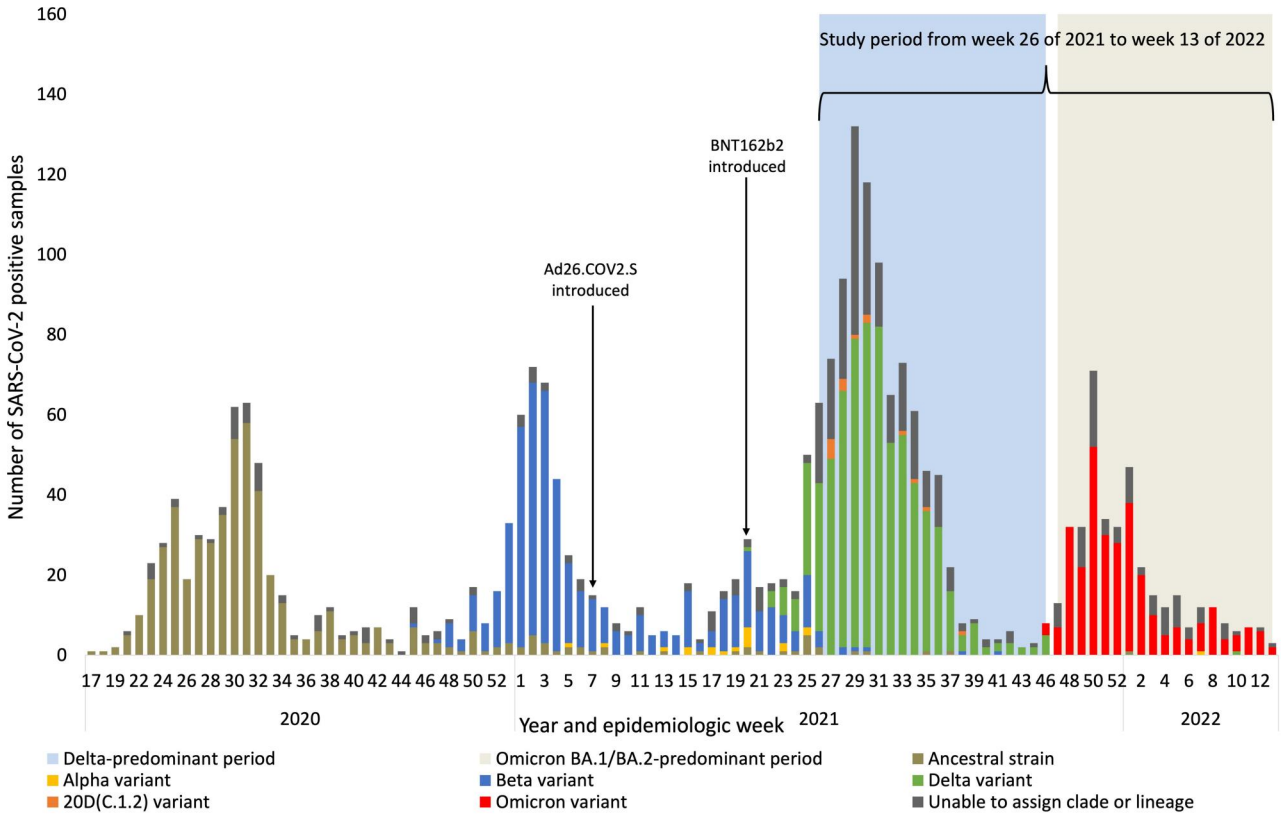

Figure 1. Number of SARS-CoV-2 cases by epidemiological week and SARS-CoV-2 variant among all adult inpatients enrolled in pneumonia surveillance in South Africa, 19 April 2020 to 31 March 2022. The BNT162b2 vaccine is an mRNA COVID-19 vaccine manufactured by Pfizer-BioNTech, and the Ad26.COV2.S vaccine is a viral vector COVID-19 vaccine manufactured by Johnson & Johnson

Table 2. Estimated BNT162b2 vaccine effectiveness against SARS-CoV-2-associated hospitalization by different periods and accounting for time since vaccination in adults aged ≥18 years enrolled in pneumonia surveillance in South Africa, 28 June 2021 to 31 March 2022

BNT162b2 (Pfizer)[a]	*n* (controls)	*N* (controls)	*n* (cases)	*N* (cases)	VE (%)	95% CI lower (%)	95% CI upper (%)
Entire period							
Fully vs not vaccinated	186	1779	38	890	51	23	68
60+ years fully vs not vaccinated	111	575	22	387	62	27	80
(HIV uninfected) fully vs not vaccinated	125	938	22	608	67	40	82
(PLHIV) fully vs not vaccinated	51	730	15	233	1	−110	53
Entire period (time since vaccination)							
14–60 days fully vaccinated	59	1779	8	890	74	40	89
61–120 days fully vaccinated	53	1779	16	890	33	−30	65
>120 days fully vaccinated	74	1779	14	890	40	−18	70
Delta variant period							
Fully vs not vaccinated	65	1060	3	445	91	52	98
60+ years fully vs not vaccinated	47	363	2	223	94	50	99
(HIV uninfected) fully vs not vaccinated	52	564	3	319	89	27	98
(PLHIV) fully vs not vaccinated	9	422	0	101	–	–	–
Delta variant period (time since vaccination)							
14–60 days fully vaccinated	37	1060	3	445	89	41	98
61–120 days fully vaccinated	21	1060	0	445	–	–	–
>120 days fully vaccinated	7	1060	0	445	–	–	–
Omicron variant period							
Fully vs not vaccinated	121	719	25	211	33	−16	62
60+ years fully vs not vaccinated	64	212	14	54	54	−8	80
(HIV uninfected) fully vs not vaccinated	73	374	13	124	55	4	79
(PLHIV) fully vs not vaccinated	42	308	12	77	−37	−246	46
Omicron variant period (time since vaccination)							
14-60 days fully vaccinated	22	719	4	211	57	−34	86
61-120 days fully vaccinated	32	719	11	211	17	−82	63
>120 days fully vaccinated	67	719	10	211	36	−45	71

All analyses did not meet the 80% power threshold.
VE, vaccine effectiveness; HIV, human immunodeficiency virus; PLHIV, people living with HIV; CI, confidence interval.
[a] The BNT162b2 vaccine is an mRNA COVID-19 vaccine manufactured by Pfizer-BioNTech.

Table 3. Estimated Ad26.COV2.S vaccine effectiveness against SARS-CoV-2-associated hospitalization by different periods and accounting for time since vaccination in adults aged ≥18 years enrolled in pneumonia surveillance in South Africa, 28 June 2021 to 31 March 2022

Ad26.COV2.S (Johnson & Johnson)[a]	*n* (controls)	*N* (controls)	*n* (cases)	*N* (cases)	VE (%)	95% CI lower (%)	95% CI upper (%)
Entire period							
Fully vs not vaccinated	94	1581	30	800	−9	−83	35
60+ years fully vs not vaccinated	20	424	7	311	16	−162	73
(HIV uninfected) Fully vs Not vaccinated	41	777	14	532	30	−52	68
(PLHIV) fully vs not vaccinated	48	700	14	219	−24	−158	40
Entire period (time since vaccination)							
14–60 days fully vaccinated	20	1581	8	800	−39	−304	52
61–120 days fully vaccinated	26	1581	6	800	44	−50	79
>120 days fully vaccinated	48	1581	16	800	−41	−174	28
delta variant period							
fully vs not vaccinated	27	945	5	400	72	−36	94
60+ years fully vs not vaccinated	7	274	3	259	31	−331	89
(HIV uninfected) fully vs not vaccinated	15	468	6	388	67	−78	94
(PLHIV) fully vs not vaccinated	11	408	2	128	76	−164	98
Delta variant period (time since vaccination)							
14–60 days fully vaccinated	13	945	4	400	−26	−430	70
61–120 days fully vaccinated	8	945	0	400	–	–	–
>120 days fully vaccinated	6	945	1	400	60	−318	96
Omicron variant period							
fully vs not vaccinated	67	636	15	191	−19	−130	39
60+ years fully vs not vaccinated	13	150	3	41	10	−370	83
(HIV uninfected) fully vs not vaccinated	26	309	6	111	13	−159	71
(PLHIV) fully vs not vaccinated	37	292	8	69	−34	−242	48
Omicron variant period (Time Since Vaccination)							
14–60 days fully vaccinated	7	636	2	191	−66	−1066	76
61–120 days fully vaccinated	18	636	1	191	78	−72	97
>120 days fully vaccinated	42	636	12	191	−80	−288	16

All analyses did not meet the 80% power threshold.
VE, vaccine effectiveness; HIV, human immunodeficiency virus; PLHIV, people living with HIV; CI, confidence interval.
[a] The Ad26.COV2.S vaccine is a viral vector COVID-19 vaccine manufactured by Johnson & Johnson.

susceptibility to BNT162b2-elicited neutralization.[32] In HIV-uninfected fully vaccinated individuals, our BNT162b2 VE estimate during Delta (89%) was similar to a Canadian study (85–92%). However, we could not reliably estimate VE in PLHIV due to small sample sizes, unlike the Canadian study that reported VE (58–90%) in this population. Apart from sample size numbers, treatment adherence and immune response variations by CD4+ counts could potentially explain this disparity, as studies in the USA and Italy reported that PLHIV with CD4+ counts <200 cell/mm^3 exhibit a lower immune response post-vaccination compared with those with CD4+ counts >500 cell/mm^3 or those HIV uninfected.[33–35] Unfortunately, our study's small sample of vaccinated PLHIV restricted further stratification by CD4+ counts.

Our BNT162b2 VE estimates during the Omicron period, and Ad26.COV2.S VE estimates during both variant periods, did not show a clear protective effect. However, the point estimates indicated some level of protection for BNT162b2 in the Omicron period and Ad26.COV2.S during the Delta period. Previous studies have reported Ad26.COV2.S VE during the Delta period, with a 67% VE reported in the Sisonke study among South African health care workers and 81% in a US study. Limited data exist against the Omicron variants; however, a Brazilian cohort study did note a 72.3% VE against hospitalization for individuals aged over 60 during the Omicron surge.[36] The reduced Ad26.COV2.S VE observed in our study may reflect waning immunity following the initial single-dose Ad26.COV2.S vaccination roll-out in South Africa from March 2021. It is also possible that the lower VE against Omicron in our study is due to prior SARS-CoV-2 infections among participants, with 1% reporting previous infections during Delta period versus 5% during Omicron, likely underestimating true infection rates. As a result, the VE estimates are now comparing vaccinated individuals (with or without previous infection) with a population consisting mostly of individuals who have already been infected with SARS-CoV-2 and may have some natural protection, rather than individuals who have not been exposed to the virus before. This suggests natural immunity could be influencing VE comparisons. Furthermore, the increase in seroprevalence in South Africa, from 47% before the Delta wave to 75% post-Delta wave, indicates undiagnosed SARS-CoV-2 infections.[37,38] Moreover, Omicron infections in South Africa included a mix of reinfections and vaccine breakthroughs, further complicating VE estimations.[39] The Omicron variant's demonstrated ability to evade neutralization by vaccinated individuals' antibodies may also play a role in the observed VE trends.[40]

Our study had several limitations. The milder clinical presentation during the Omicron BA.1/BA.2-predominant period and relatively small sample size, partly due to low vaccine coverage, reduced statistical power and yielded wide confidence intervals for some endpoints, including Ad26.COV2.S VE by HIV status. Additionally, self-reported vaccination and SARS-CoV-2 infection histories could have diminished the accuracy of VE estimates, similar to influenza studies.[41] Also unmeasured confounders, including variations in testing practices and shifts in the prioritization of different

population groups, could have biased our estimates. For instance, early vaccination of higher-risk individuals with Ad26.COV2S and then later BNT162b2 might have led to confounding by indication, resulting in an overestimation of VE, whereas lower vaccine uptake in high-risk groups or changes in exposure risk due to policy changes could have resulted in an underestimation VE. Furthermore, unmeasured health factors such as frailty influencing both vaccine uptake and COVID-19 severity, if unevenly distributed between vaccinated and unvaccinated groups, might have skewed our VE estimates. Moreover, the evolving COVID-19 testing guidelines raised concerns about the potential misclassification of prior infections over time. Whereas testing for SARS-CoV-2 was widespread in South Africa in 2020 for both mild and severe illness, practices had evolved by 2022, making testing non-mandatory, which could have led to under-reporting of infections. Although we attempted to mitigate these potential biases through stratification, careful selection of the study period and reliance on sentinel surveillance for timely VE estimates, the possibility of residual confounding remained.

The national pneumonia surveillance sites were selected to represent the public health care system catering to the majority of the South African population, particularly those from lower socioeconomic backgrounds, were distributed across different provinces and included various health.care levels. However, limitations inherent in its sentinel nature and the potential bias in capturing individuals solely within the public health care system should be considered, but our methodology and site selection aimed to minimize such biases. Last, despite ongoing quality checks, limitations in data completion and potential reporting delays remain notable challenges in our study.

A strength of our study is the application of consistent case definitions and testing strategy throughout the study period. Furthermore, whereas the 10 sentinel sites may not fully represent the national population, they aimed to capture the public health care system used by most South Africans, including groups often under-represented in clinical trials like older adults and PLHIV. This provided a valuable real-world assessment of the SARS-CoV-2 vaccine performance in diverse populations. Moreover, continuous comparisons with national data further support the representativeness of our findings, though health care access barriers could not be fully accounted for.

Conclusion

In conclusion, we found that two BNT162b2 vaccine doses were effective against SARS-CoV-2-associated hospitalization in all and in HIV-uninfected individuals across the entire and the Delta-predominant periods. Extended time series may further elucidate VE in PLHIV. Nevertheless, these estimates affirm sentinel surveillance systems utility in assessing VE of COVID-19 vaccines, particularly in resource-limited settings.

Ethics approval

The study protocol was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M140824). This study was reviewed by the US Centers for Disease Control and Prevention (CDC) and was carried out in accordance with US federal law and CDC policy (see for example 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. 241 (d); 5 U.S.C. 552a; 44 U.S.C. 3501 et seq.). All participants provided written consent.

Data availability

Data used in this manuscript are available upon reasonable request. Proposals should be directed to cherylc@nicd.ac.za.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

Concept and design of the study: N.C., S.W., A.v.G., L.F., P. M., A.M.S., C.C. Analysis and interpretation: N.C., S.W., A. v.G., N.W., M.P., F.M., M.J.G., J.N., E.V., H.D., M.M., L. F., P.M., A.M.S., C.C. Accessed and verified the underlying data: N.C., S.W., A.v.G., C.C. Drafted the article: N.C., S. W., C.C. All authors critically reviewed the article.

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Conflict of interest

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