Estimation of vaccine effectiveness against SARS-CoV-2-associated hospitalisation using sentinel surveillance in South Africa, a test-negative case-control study

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Research Article

Abstract

Background

COVID-19 vaccine effectiveness (VE) studies leveraging systematic surveillance in sub-Saharan Africa are limited. We aimed to assess BNT162b2 and Ad26.COV2.S VE against SARS-CoV-2-associated hospitalisation in South African individuals aged ≥ 18 years.

Methods

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

Results

A total of 985 cases and 1,963 controls were included. Thirty-eight (3.9%) cases and 186 (9.5%) controls were fully vaccinated with BNT162b2; 30 (3.0%) cases and 94 (4.8%) controls were fully vaccinated with Ad26.COV2.S. BNT162b2 VE against SARS-CoV-2-associated hospitalisation over Delta and Omicron BA.1/BA.2 periods was 77% (95% CI: 26%;93%) and 38% (-9%;64%), respectively. Ad26.COV2.S VE against hospitalisation over Delta and Omicron BA.1/BA.2 periods was 47% (-57%;82%), and – 19% (-128%;37%), respectively. BNT162b2 VE against hospitalisation over Delta period was 84% (37%;96%) and 76% (21%;93%) among adults aged ≥ 60 years and HIV-uninfected, respectively.

Conclusions

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

KEY MESSAGES

- Limited Sub-Saharan African research on BNT162b2 and Ad26.COV2.S vaccine effectiveness (VE), especially in resource limited settings, with different SARS-CoV-2 variants and focusing on high-risk populations such as people living with HIV (PLHIV) and older adults.
- Our study leveraged a test-negative case-control study design within the national pneumonia sentinel syndromic surveillance programme to estimate BNT162b2 and Ad26.COV2.S VE against SARS-CoV-2-associated hospitalisation in South Africa,.
- Our results indicate that the BNT162b2 vaccine effectiveness against SARS-CoV-2-associated hospitalisation during the Delta period for adults aged ≥18 years, ≥60 years, and HIV-uninfected adults, while Ad26.COV2.S did not show significant effectiveness.
- Our findings offer valuable insights into real-world vaccine performance in resource-limited settings and emphasize the utility of sentinel surveillance for estimating VE.

INTRODUCTION

By April 2, 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 rollout started in February 2021 prioritizing frontline and healthcare workers, followed by different age groups and those with high-exposure occupations, and concluding with adults aged 18–34 years before the Delta variant wave dissipated. As of the 3rd of 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 VE estimates for the foreseeable future. As countries move away from policies advocating universal testing for SARS-CoV-2 among hospitalised 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 hospitalisation in adults aged ≥ 18 years in South Africa using data from national sentinel surveillance for pneumonia.

METHODS

Surveillance programme and study design

We conducted a TND study within the pneumonia sentinel syndromic surveillance programme in South Africa to estimate the VE of the BNT162b2 and Ad26.COV2.S vaccines. Eligible adults were those aged ≥ 18 years, who met the surveillance case definition of either a physician-diagnosed lower respiratory tract illness (LRTI) (e.g. bronchiolitis, pneumonia, bronchitis and pleural effusion) or suspected COVID-19, had complete SARS-CoV-2 rRT-PCR results and vaccination status between 17 May 2021 and 31 March 2022, and were recommended to receive SARS-CoV-2 vaccines according to the South African vaccination roll-out plan at the time of their enrolment. Details of the vaccination roll-out plan are described in the supplementary materials, and comprehensive descriptions of the programme and laboratory testing procedures have been previously published.[17,21-24]

Briefly, in response to the first SARS-CoV-2 case in South Africa on 5 March 2020, the existing active pneumonia sentinel surveillance programme, initially established in 2009 to monitor influenza virus and other respiratory pathogens, was expanded to incorporate molecular testing and sequencing for SARS-CoV-2. To increase participant numbers for VE estimation, three additional sentinel surveillance public hospitals were added to the existing seven surveillance hospitals, resulting in a total of ten hospitals across six provinces. The COVID-19 vaccination status was obtained through self-reporting, vaccination cards, hospital vaccine registers, or the official South African COVID-19 Electronic Vaccination Data System (EVDS) when available. HIV status was obtained from the patient's hospital file or through pre-test counselling and testing. Previous SARS-CoV-2 infections were self-reported. Enrolled patients were followed until their discharge, transfer, or death. Surveillance officers collected nasopharyngeal swabs from all participants, placing them in universal transport medium. Swabs were stored in a

cooler box on ice at 4–8°C for transportation to the National Institute for Communicable Diseases (NICD) within 72 hours of collection.

Laboratory procedures

Nucleic acids were obtained from a 200µl 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 real-time reverse transcription polymerase chain reaction (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.

Definition of cases, controls, and variables

Cases were eligible individuals who tested positive for SARS-CoV-2 by rRT-PCR, while controls were those who tested negative. COVID-19 vaccination status was categorised into three groups: fully vaccinated, partially vaccinated and not vaccinated. Fully vaccinated was defined as having received ≥ 1 dose of the Ad26.COV2.S vaccine or two doses of the BNT162b2 vaccine at least 14 days before symptom onset. Partially vaccinated was defined as receiving any vaccine dose but not meeting the criteria to be classified as fully vaccinated. This included people who had received a single dose of BNT162b2 vaccine or any vaccine dose, provided that 14 days had not passed since their vaccination. Not vaccinated was defined as receiving no vaccine doses. Patients who received combinations of the Ad26.COV2.S and BNT162b2 vaccines were excluded (N = 3). Time since vaccination was calculated as the number of days from the last received vaccine dose to the symptom onset date. Time since vaccination was grouped into 5 categories: not vaccinated, partially vaccinated, 14–60 days since becoming fully vaccinated, 61–120 days since becoming fully vaccinated, and > 120 days since becoming fully vaccinated.

Variants and epidemic wave periods

Positive SARS-CoV-2 specimens were categorised 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 sequenced specimens within the surveillance network in a week. The study period included two epidemic waves: the Delta-predominant period (2021 weeks 20–47, corresponding to 17 May – 28 November 2021), and Omicron BA.1/BA.2-predominant period (2021 week 48–2022 week 13, corresponding to 29 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%.[26]

Statistical analysis

Patient characteristics such as demographic and clinical data were described for cases and controls and compared using the Chi-squared test. Multivariable logistic regression was used to determine the VE of the BNT162b2 and Ad26.COV2.S vaccines against SARS-CoV-2 associated-hospitalisation 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 determine the VE of the BNT162b2 vaccine against SARS-CoV-2 associated-hospitalisation stratified by HIV status over the three abovementioned periods. PLHIV was further categorised into three groups: no severe immunosuppression (CD4 + count > 200 cell/mm3 or viral load ≤ 10,000 copies/mL), severe immunosuppression (CD4 + count ≤ 200 cell/mm3 or viral load > 10,000 copies/mL), and missing immunosuppression information (missing CD4 + count and viral load results). Available confounders known to be associated with vaccine effectiveness including age group, sex, race, month of admission, previous self-reported SARS-CoV-2 infection, HIV status (HIV uninfected, PLHIV and unknown), presence of at least one underlying condition (yes, no) and province were adjusted for during the analysis.[27] Propensity scores were not used due to the small

sample size. VE was estimated as a percentage derived from the formula $(1 - oddsratio)x100\%$, where the odds ratio (OR) was obtained from the multivariable logistic regression models. VE was not reported for partially vaccinated individuals because of small numbers or for any subgroups where the number of cases was zero. The level of statistical significance was set at P< 0.05. Stata version 17 (StataCorp Limited, College Station, TX) was used for analysis.

Ethics

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 e.g., 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.

RESULTS

Characteristics of cases and controls

2,948 hospitalised individuals met the inclusion criteria, with 985 (33.4%) testing positive for SARS-CoV-2 (cases) and 1,963 (66.6%) testing negative (controls) (Fig. 1). The majority of cases and controls were aged ≥ 60 years, female or enrolled during the Delta-predominant period (Table 1). Twenty-six percent (258/985) of cases and 40.9% (803/1,963) of controls were PLHIV. Among these PLHIV, 22.9% (59/258) of cases and 32.3% (259/803) of controls had CD4 + cell counts ≤ 200 or viral loads > 10,000 copies/mL.

Table 1

Characteristics of hospitalised adults aged ≥ 18 years eligible for SARS-CoV-2 vaccination who tested positive (cases) and negative (controls) for SARS-CoV-2 at ten pneumonia surveillance sentinel hospitals in South Africa, 17 May 2021 to 31 March 2022.

	Total (N = 2,948) n (%)	Cases (N = 985) n (%)	Controls (N = 1,963) n (%)	p-value
Age groups (years)				
18−34	517 (17.5)	140 (14.2)	377 (19.2)	< 0.001
35−49	745 (25.3)	182 (18.5)	563 (28.7)	
50−59	567 (19.2)	212 (21.5)	355 (18.1)	
≥60	1119 (38.0)	451 (45.8)	668 (34.0)	
Sex				
Male	1311 (44.5)	382 (38.8)	929 (47.3)	< 0.001
Female	1637 (55.5)	603 (61.2)	1034 (52.7)	
Race				
Black	2409 (81.7)	765 (77.7)	1644 (83.7)	< 0.001
Non-Black	537 (18.2)	219 (22.2)	318 (16.2)	
Unspecified	2 (0.1)	1 (0.1)	1 (0.1)	
Overall vaccination status*				
Not vaccinated	2,363 (80.2)	821 (83.4)	1,542 (78.6)	< 0.001
BNT162b2 partially vaccinated	215 (7.3)	91 (9.2)	124 (6.3)	
Ad26.COV2.S partially vaccinated	22 (0.7)	5 (0.5)	17 (0.9)	
BNT162b2 fully vaccinated	224 (7.6)	38 (3.9)	186 (9.5)	
Ad26.COV2.S fully vaccinated	124 (4.2)	30 (3.0)	94 (4.8)	
HIV Status				
Uninfected	1707 (57.9)	670 (68.0)	1037 (52.8)	< 0.001
PLHIV	1061 (36.0)	258 (26.2)	803 (40.9)	
Unknown	180 (6.1)	57 (5.8)	123 (6.3)	
PLHIV (N = 1061; N = 258; N = 803)				
CD4 + > 200 cell/mm3 or VL ≤ 10,000 copies/mL	521 (49.1)	138 (53.5)	383 (47.6)	0.016
CD4 + ≤ 200 cell/mm3 or VL > 10,000 copies/mL	318 (30.0)	59 (22.9)	259 (32.3)	
Abbreviations: Viral load (VL).				

#Vaccination status is 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).

*Underlying conditions included cirrhosis liver, valvular heart disease, organ transplant, splenectomy, immunoglobulin, nephrotic, 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, COPD/emphysema, stroke, heart failure, sinusitis, sickle cell disease, burns, malnutrition, seizure disorder, prematurity, congenital heart disease, asthma, hypertension, currently pregnant, previous TB infection, and current TB infection.

	Total (N = 2,948) n (%)	Cases (N = 985) n (%)	Controls (N = 1,963) n (%)	p-value
Age groups (years)				
CD4 + missing and VL missing	222 (20.9)	61 (23.6)	161 (20.1)	
Previous self-reported SARS-CoV-2 infection				
No	1245 (42.2)	352 (35.7)	893 (45.5)	< 0.001
Yes	62 (2.1)	15 (1.5)	47 (2.4)	
Unknown	1641 (55.7)	618 (62.7)	1023 (52.1)	
Underlying condition#				
No	1238 (42.0)	408 (41.4)	830 (42.3)	0.655
Yes	1710 (58.0)	577 (58.6)	1133 (57.7)	
Enrolment period				
Delta-predominant	1,925 (65.3)	700 (71.1)	1,225 (62.4)	< 0.001
Omicron BA.1/BA.2-predominant	1,023 (34.7)	285 (28.9)	738 (37.6)	
Province				
Gauteng	847 (28.7)	221 (22.4)	626 (31.9)	< 0.001
KwaZulu-Natal	665 (22.6)	250 (25.4)	415 (21.1)	
Mpumalanga	489 (16.6)	121 (12.3)	368 (18.8)	
North West	444 (15.1)	191 (19.4)	253 (12.9)	

Abbreviations: Viral load (VL).

#Vaccination status is 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).

*Underlying conditions included cirrhosis liver, valvular heart disease, organ transplant, splenectomy, immunoglobulin, nephrotic, 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, COPD/emphysema, stroke, heart failure, sinusitis, sickle cell disease, burns, malnutrition, seizure disorder, prematurity, congenital heart disease, asthma, hypertension, currently pregnant, previous TB infection, and current TB infection.

	Total (N = 2,948) n (%)	Cases (N = 985) n (%)	Controls (N = 1,963) n (%)	p-value
Age groups (years)				
Western Cape	503 (17.1)	202 (20.5)	301 (15.3)	
Abbreviations: Viral load (VL).				
#Vaccination status is 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).				
*Underlying conditions included cirrhosis liver, valvular heart disease, organ transplant, splenectomy, immunoglobulin, nephrotic, 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, COPD/emphysema, stroke, heart failure, sinusitis, sickle cell disease, burns, malnutrition, seizure disorder, prematurity, congenital heart disease, asthma, hypertension, currently pregnant, previous TB infection, and current TB infection.				

Vaccination status was ascertained through self-report, with 22.9% (134/585) verified by vaccine card and a further 12.1% (71/585) verified through vaccine registry. Overall, 19.8% (585/2,948) were vaccinated and 80.2% (2,363/2,948) were unvaccinated. Among those vaccinated 38.3% (224/585) and 21.2% (124/585) were fully vaccinated with the BNT162b2 and Ad26.COV2.S vaccines, respectively and 40.5% (237/585) were partially vaccinated. Among the cases, 16.6% (164/985) were vaccinated, with 41.5% (68/164) fully vaccinated and 58.5% (96/164) partially vaccinated. Of the cases that were fully vaccinated (n = 68), 55.9% (38/68) and 44.1% (30/68) were vaccinated with the BNT162b2 and Ad26.COV2.S vaccines, respectively. Among the controls, 21.4% (421/1,963) were vaccinated, with 66.5% (280/421) fully vaccinated and 33.5% (141/421) partially vaccinated. Of the controls that were fully vaccinated (n = 280), 66.4% (186/280) and 33.6% (94/280) were vaccinated with the BNT162b2 and Ad26.COV2.S vaccines, respectively. There were statistically significant differences between cases and controls regarding age group, sex, race, vaccination status, HIV status, self-reported previous SARS-CoV-2 infection history, enrolment period, and province (Table 1).

SARS-CoV-2 variant trends

Of 985 SARS-CoV-2 positive specimens available for variant characterisation throughout the study, 8 (0.8%) were ancestral strain, 4 (0.4%) Alpha, 36 (3.7%) Beta, 468 (47.5%) Delta, 7 (0.7%) 20(DC.1.2), 231 (23.5%) Omicron BA.1/BA.2, and 231 (23.5%) could not be assigned to a variant because of low viral load (Fig. 2).

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

Adjusted VE of the BNT162b2 vaccine against SARS-CoV-2-associated hospitalisation was 50% (95% confidence interval [CI]: 23%−67%) during the entire study period, 77% (95% CI: 26%−93%) during the Delta-predominant period, and 38% (95% CI: -9%−64%) during the Omicron BA.1/BA.2-predominant period (Fig. 3). Adjusted VE of the Ad26.COV2.S vaccine against SARS-CoV-2-associated hospitalisation was − 14% (95% CI: -84%−30%) during the entire study period, 47% (95% CI: -57%−82%) during the Delta-predominant period, and − 19% (95% CI: -128%−37%) during the Omicron BA.1/BA.2-predominant period.

Among patients aged ≥ 60 years, adjusted VE of the BNT162b2 vaccine against SARS-CoV-2-associated hospitalisation was 61% (95% CI: 31%−78%) during the entire study period, 84% (95% CI: 37%−96%) during the Delta-predominant period, and 45% (95% CI: -3%−71%) during the Omicron BA.1/BA.2-predominant period (Fig. 3). Among this same age group, adjusted VE of the Ad26.COV2.S vaccine against SARS-CoV-2-associated hospitalisation was 4% (95% CI: -162%−65%) during the entire study period, 27% (95% CI: -333%−88%) during the Delta-predominant period, and 29% (95% CI: -87%−73%) during the Omicron BA.1/BA.2-predominant period.

Among HIV uninfected patients, adjusted VE of the BNT162b2 vaccine against SARS-CoV-2-associated hospitalisation was 66% (95% CI: 42%−81%) during the entire study period and 76% (95% CI: 21%−93%) during the Delta-predominant period (Fig. 3).

Numbers were too small to evaluate BNT162b2 VE among PLHIV in the variant-predominant periods or Ad26.COV2.S VE against SARS-CoV-2-associated hospitalisation stratified by HIV status.

BNT162b2 VE for fully-vaccinated participants 14−60 days after vaccination was 72% (95% CI: 37%−87%) during the entire period and 73% (95% CI: 10%−92%) during the Delta-predominant period (Fig. 4). BNT162b2 VE more than 60 days after vaccination and during the Omicron BA.1/BA.2-predominant period as well as Ad26.COV2.S VE was not significant.

DISCUSSION

In this study, we used a TND to analyse national pneumonia surveillance data and assess the VE of the BNT162b2 and Ad26.COV2.S vaccines against SARS-CoV-2-associated hospitalisation. Our findings showed that two doses of the BNT162b2 vaccine were effective in preventing SARS-CoV-2-associated hospitalisation in all adult inpatients, those aged ≥ 60 years, and those who were HIV-uninfected during both the entire study period and Delta-predominant period. Furthermore, we observed that being fully vaccinated with the BNT162b2 vaccine 14 to 60 days after vaccination was effective against hospitalisation in all adult inpatients during the same periods. However, VE appeared to decrease with increasing time since vaccination.

Our BNT162b2 VE estimate (77%) during the Delta-predominant period was slightly lower than a South African study which estimated a VE of 92% using a TND analysis of private medical insurance data with 14,673 COVID-19 admissions between 17 May 2021 and 23 September 2021.[15] Possible reasons include differences in study populations between our and their study. In our study, individuals who access care at public hospitals may have significant differences in demographics, risk factors, comorbidities, age distribution and vaccine uptake compared to the latter study population which accesses care from private hospitals. Similarly, our VE estimate 14−60 days after the second dose of BNT162b2 (72%) was lower compared to the abovementioned study which reported an estimate of 94% 14 days after the second dose.[15] When compared to other countries, our study's BNT162b2 VE estimates against hospitalisation during the Delta variant period were lower but comparable to Thailand (88%), Japan (> 86%), Israel (97%), and the United States (90%), but higher than Singapore (45%).[28−32] This is consistent with the fact that the Delta variant has been shown to be susceptible to BNT162b2-elicited neutralisation, supporting our findings.[33]

Stratifying by HIV status, our study's BNT162b2 VE in HIV uninfected fully vaccinated individuals of 66% was also comparable to a Canadian study that reported VE of 85%−92% in an HIV-negative cohort; however, the Canadian study period was not explicitly restricted to the Delta variant period but rather the period before Omicron emergence which may have included multiple variants. The same Canadian study demonstrated significant VE in PLHIV ranging from 58−90%, whereas our study did not show significant VE in PLHIV. One possible reason for this difference could be variations in treatment adherence in our population, as other studies in the United States and Italy have reported that patients with CD4 + cell counts < 200 cell/mm^3 had a significantly lower immune response after vaccination compared to those with CD4 + cell counts > 500 cell/mm^3 or those HIV uninfected.[34−36] Unfortunately, due to the limited number of vaccinated PLHIV in our study, it was not possible to further stratify our findings by CD4 + cell counts.

Our estimates of the VE of the BNT162b2 vaccine during the Omicron BA.1/BA.2-predominant period and the Ad26.COV2.S vaccine during both the Delta- and Omicron BA.1/BA.2-predominant periods were not statistically significantly different from no effect. Point estimates of VE for BNT162b2 VE in the Omicron period and Ad26.COV2.S in the Delta period were, however, above zero. Previous studies have reported significant VE for Ad26.COV2.S VE during the Delta variant period including the Sisonke study in South African healthcare workers (67%) and a study conducted in the United States (81%). Unfortunately, there were no published single dose Ad26.COV2.S VE studies using TND against the Omicron variants for further comparison; however, a Brazilian cohort design study that used registry data reported a VE against hospitalisation of 72.3% in those aged 60 years and above during the period of Omicron dominance.[37] Reasons for our findings of Ad26.COV2.S VE against hospitalisation over Delta and Omicron BA.1/BA.2 periods of 47% and − 19%, respectively, may be due to waning immunity, as single dose Ad26.COV2.S vaccination roll-out began in March 2021 in South Africa. Another possible reason for the fact that VE was not significant against Omicron in our study is that most of the enrolled patients may have been previously infected with SARS-CoV-

2 by the time they were enrolled. As a result, the VE estimates are now comparing vaccinated individuals (with or without previous infection) to 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 is supported by the fact that 1% reported previous infection in the Delta-predominant period versus 5% in the Omicron-predominant period, and these percentages likely underrepresent actual case numbers. Importantly, the seroprevalence in South Africa estimated from blood donors before the third wave dominated by the Delta variant was 47%, which markedly increased to 75% after the Delta wave, indicating that the vast majority of SARS-CoV-2 infections in South Africa were not diagnosed.[38,39] Moreover, according to a recent study, a significant proportion of the Omicron infections observed in South Africa were found to be reinfections and vaccine breakthrough cases, which adds an additional layer of complexity to our efforts to estimate VE.[40] Additionally the Omicron variants' ability, as demonstrated in vitro, to evade neutralisation by antibodies from the sera of vaccinated individuals could have contributed to low VE.[41]

There were limitations to our study. The less severe disease in the Omicron BA.1/BA.2-predominant period together with the relatively small sample size which was partly due to low vaccine coverage resulted in reduced power and wide confidence intervals for some of the endpoints. These endpoints included BNT162b2 VE in PLHIV during the Delta-predominant period, by HIV status during the Omicron BA1/BA.2-predominant period as well as Ad26.COV2.S VE by HIV status across all three periods. Most of the enrolled patients self-reported their vaccination status and their previous SARS-CoV-2 infection, which as previously reported for influenza VE studies can underestimate findings by as much as 16%.[42] Lastly, our estimates may have been biased by residual confounding factors such as testing practices, socioeconomic status, high-risk groups including health care workers or immunocompromised individuals, and time-varying policy changes, including prioritisation of different population groups, relaxation of restrictions and implementation of non-pharmaceutical interventions.

In conclusion, we found that two doses of the BNT162b2 vaccine were effective against SARS-CoV-2-associated hospitalisation in all adults and HIV-uninfected individuals during both the entire study and Delta-predominant periods. Future evaluations could use longer time series to examine VE among PLHIV. Nevertheless, these estimates demonstrate that sentinel surveillance systems can be used to determine VE of COVID-19 vaccines, especially in resource-limited settings.

Declarations

Conflict of interest

Author contributions

Conception and design of the study: NC, SW, AvG, LF, PM, AMS, CC

Analysis and interpretation: NC, SW, AvG, NW, MP, FM, MJG, JN, EV, HD, MM, LF, PM, AMS, CC

Accessed and verified the underlying data: NC, SW, AvG, CC

Drafted the Article: NC, SW, CC

All authors critically reviewed the Article.

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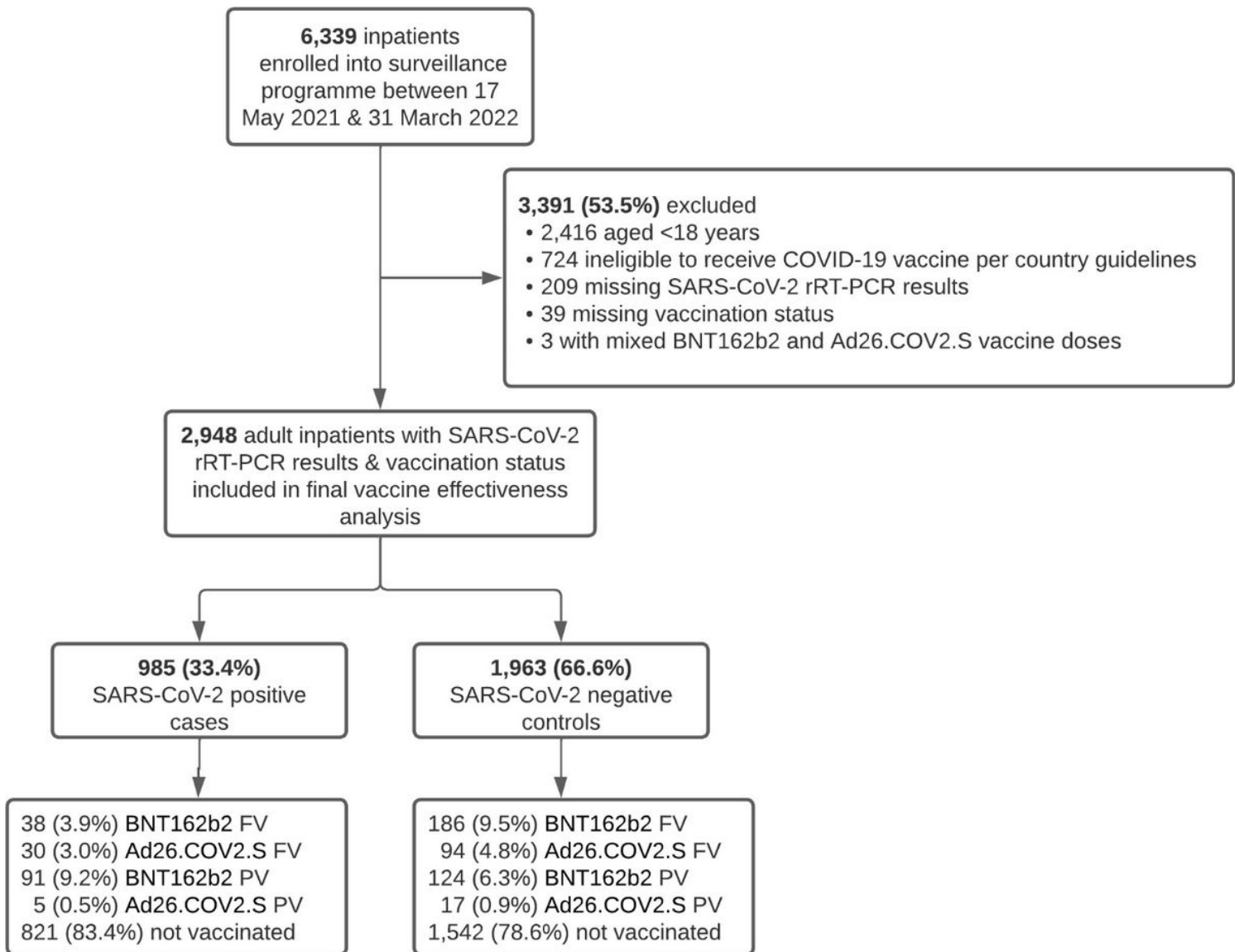
Figures

Figure 1

Flowchart of selection of study participants.

Abbreviations: Fully vaccinated (FV), Partially vaccinated (PV)
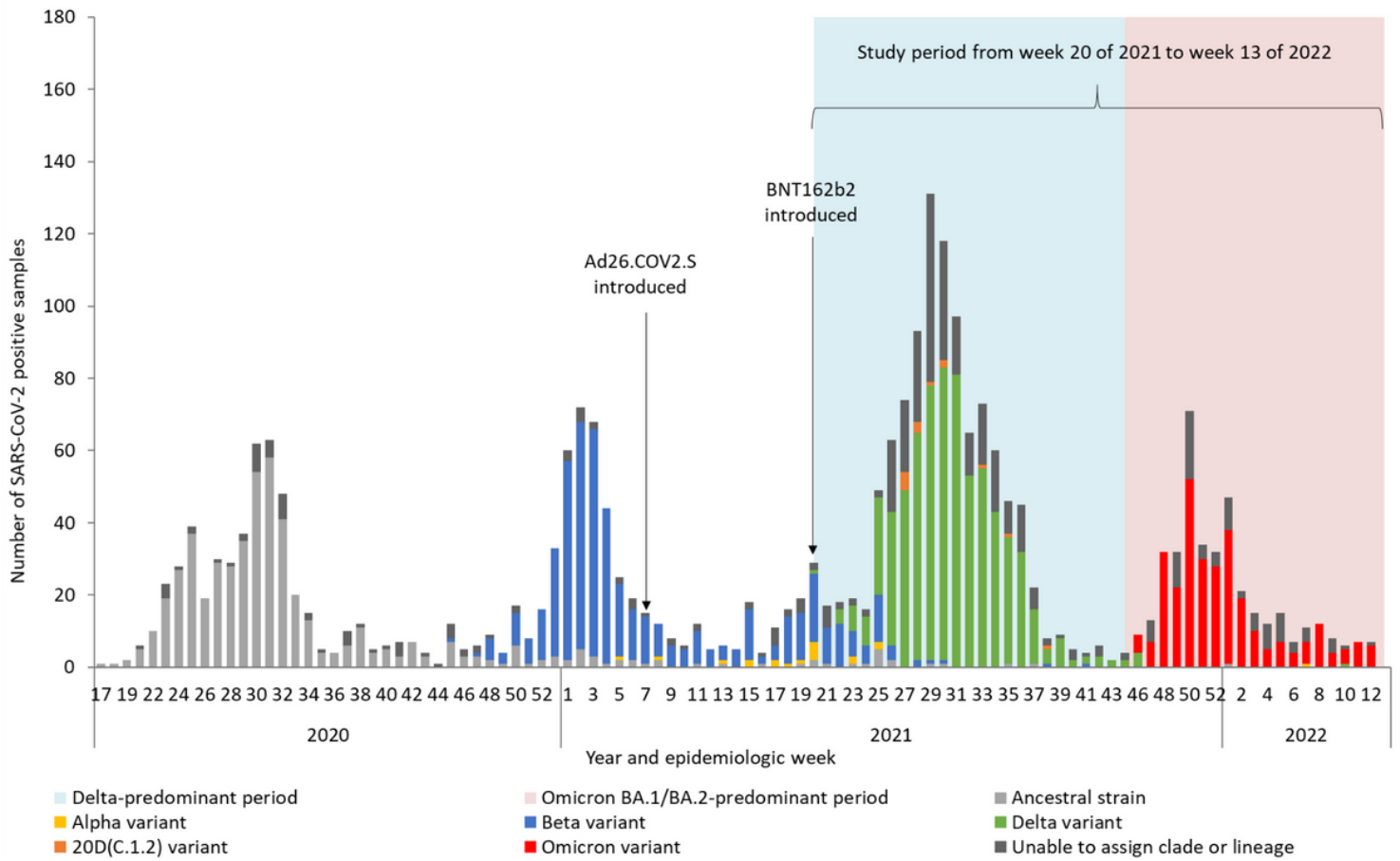
Figure 2

Number of SARS-CoV-2 cases by epidemiological week and SARS-CoV-2 variant among all inpatients enrolled in pneumonia surveillance in South Africa, 19 April 2020 to 31 March 2022
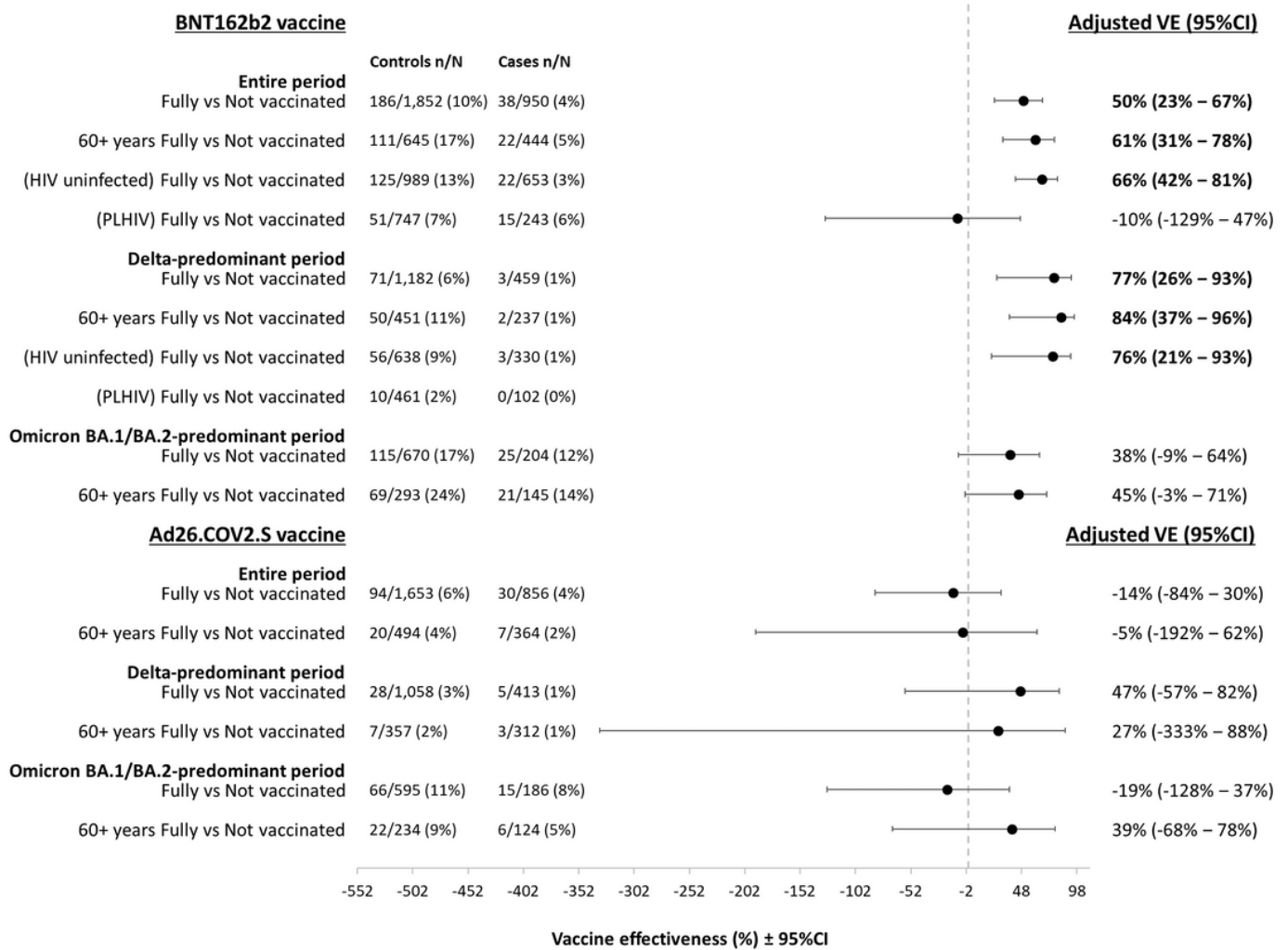
BNT162b2 vaccine

	Controls n/N	Cases n/N	Adjusted VE (95%CI)
Entire period			
Fully vs Not vaccinated	186/1,852 (10%)	38/950 (4%)	**50% (23% – 67%)**
60+ years Fully vs Not vaccinated	111/645 (17%)	22/444 (5%)	**61% (31% – 78%)**
(HIV uninfected) Fully vs Not vaccinated	125/989 (13%)	22/653 (3%)	**66% (42% – 81%)**
(PLHIV) Fully vs Not vaccinated	51/747 (7%)	15/243 (6%)	-10% (-129% – 47%)
Delta-predominant period			
Fully vs Not vaccinated	71/1,182 (6%)	3/459 (1%)	**77% (26% – 93%)**
60+ years Fully vs Not vaccinated	50/451 (11%)	2/237 (1%)	**84% (37% – 96%)**
(HIV uninfected) Fully vs Not vaccinated	56/638 (9%)	3/330 (1%)	**76% (21% – 93%)**
(PLHIV) Fully vs Not vaccinated	10/461 (2%)	0/102 (0%)	
Omicron BA.1/BA.2-predominant period			
Fully vs Not vaccinated	115/670 (17%)	25/204 (12%)	38% (-9% – 64%)
60+ years Fully vs Not vaccinated	69/293 (24%)	21/145 (14%)	45% (-3% – 71%)

Ad26.COV2.S vaccine

	Controls n/N	Cases n/N	Adjusted VE (95%CI)
Entire period			
Fully vs Not vaccinated	94/1,653 (6%)	30/856 (4%)	-14% (-84% – 30%)
60+ years Fully vs Not vaccinated	20/494 (4%)	7/364 (2%)	-5% (-192% – 62%)
Delta-predominant period			
Fully vs Not vaccinated	28/1,058 (3%)	5/413 (1%)	47% (-57% – 82%)
60+ years Fully vs Not vaccinated	7/357 (2%)	3/312 (1%)	27% (-333% – 88%)
Omicron BA.1/BA.2-predominant period			
Fully vs Not vaccinated	66/595 (11%)	15/186 (8%)	-19% (-128% – 37%)
60+ years Fully vs Not vaccinated	22/234 (9%)	6/124 (5%)	39% (-68% – 78%)

x-axis: -552 -502 -452 -402 -352 -302 -252 -202 -152 -102 -52 -2 48 98

Vaccine effectiveness (%) ± 95%CI

Figure 3

Estimated BNT162b2 and Ad26.COV2.S VE against SARS-CoV-2 associated-hospitalisation in adults aged ≥18 years enrolled in pneumonia surveillance in South Africa, 17 May 2021 to 31 March 2022.
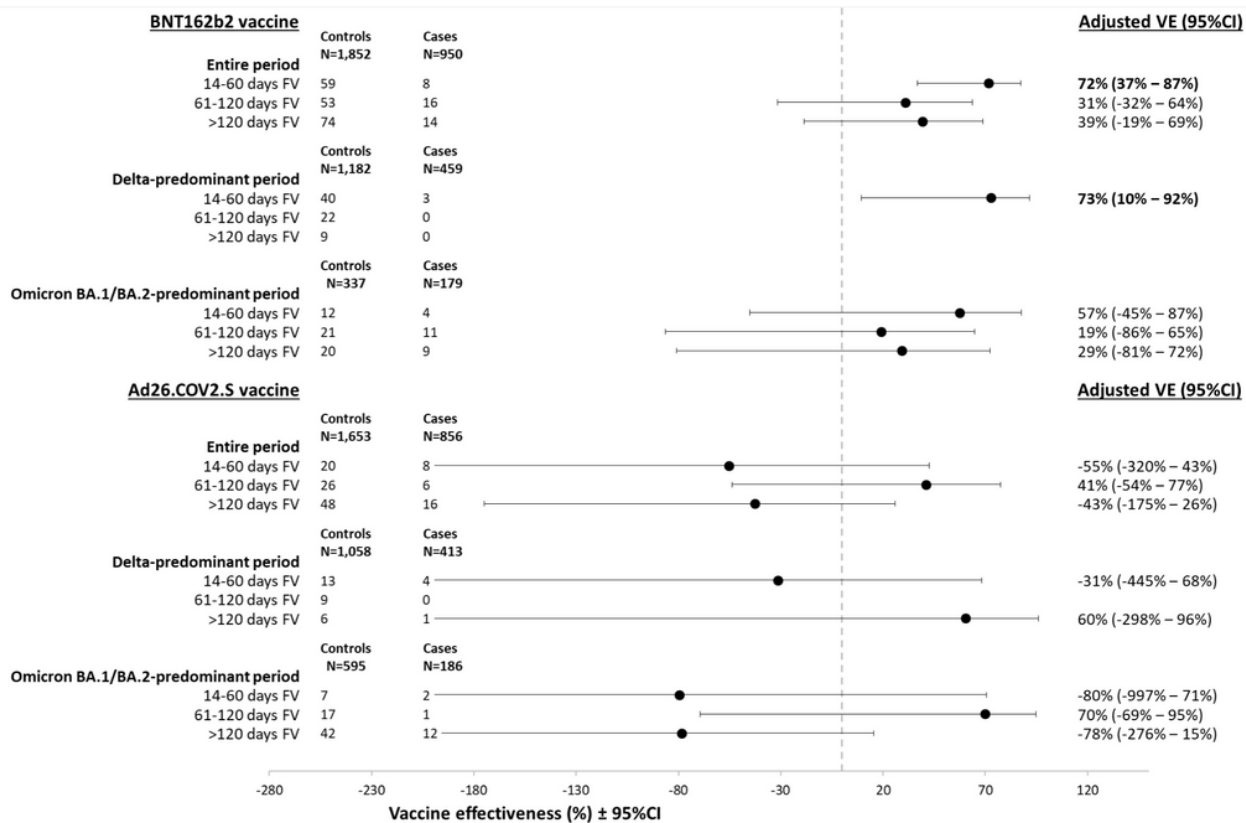
Figure 4

Estimated BNT162b2 and Ad26.COV2.S VE against SARS-CoV-2 associated-hospitalisation accounting for time since vaccination in adults aged ≥18 years enrolled in pneumonia surveillance in South Africa, 17 May 2021 to 31 March 2022

Abbreviations: Fully vaccinated (FV)

Supplementary Files

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