Effectiveness of BNT162b2 and Ad.COV2.S vaccines against COVID-19-related hospitalisation among adult members of a private health insurance scheme in South Africa during the Delta and Omicron periods: a test-negative case-control study

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Abstract

Background

COVID-19 vaccine effectiveness estimates from Africa are limited. These data can guide decisions on selecting priority groups in vaccine programs. This study estimated VE for BNT162b2 and Ad26.COV2.S against COVID-19-related hospitalisation, stratified by age group, time since vaccination and HIV-infection status for three SARS-CoV-2 surges in South Africa (driven by the delta, omicron BA.1 and omicron BA.4/5 variants) among ≥ 18 years old.

Methods

We applied a test-negative case-control design to hospitalisations for acute respiratory infections amongst members of a large medical scheme. Individuals receiving a single dose of Ad26.COV2S or two-doses of BNT162b2 were considered fully vaccinated and compared to unvaccinated individuals. Logistic regression models adjusted for age, comorbidities and documentation of previous SARS-CoV-2 infection, were used to calculate VE.

Results

BNT162b2 was protective against COVID-19-related hospitalisation for all variant periods (VE 89.3% (95% CI, 85.9−91.9) for delta, reduced to 31.4% (95% CI, 19.1−41.9) and 22.7% (95% CI, 2.2−38.9) for omicron BA.1 and BA.4/5 respectively). VE estimates for Ad26.COV2.S, although lower than BNT162b2, were protective for all periods (48.8% (95% CI, 39.6−56.5), 19.8% (95% CI, 5.8−31.6) and 45.0% (95% CI, 29.8−57.0)). Protection was similar amongst those ≥ 60 years and younger age groups, and among people living with HIV and HIV-uninfected individuals.

Conclusion

Vaccination with either BNT162b2 or Ad26.COV2.S offered significant protection against COVID-19-related hospitalisation in PLWH and adults over the age of 60 years and therefore is an effective means of reducing severe outcomes in these high-risk populations in South Africa. VE against BA.4/5 waned with time since vaccination suggesting boosters may be necessary.

Key Points

- BNT162b2 and Ad26.COV2.S were protective against COVID-19-related hospitalisation for all variant periods.
- Protection was similar amongst ≥60 years and younger groups, and among PLWH and HIV-uninfected individuals.
- Vaccination is effective in reducing severe outcomes in high-risk populations in South Africa.

Background

Since the first case of COVID-19 was reported in South Africa (SA) on 5 March 2020[1], there have been five surges of infections, each driven by a different SARS-CoV-2 variant. As of 25 March 2023 there had been 4 072 533 laboratory-confirmed cases and 102 595 reported COVID-19-related deaths, although these estimates are likely an underestimation of the true numbers[2,3]. Two COVID-19 vaccines, namely Comirnaty BNT162b2 (Pfizer Laboratories (Pty) Ltd) and Ad26.COV2.S (Janssen Johnson & Johnson), were introduced in SA. Ad26.COV2.S was introduced for healthcare workers (HCWs) in February 2021 through the Sisonke program (a single-arm, open-label, phase 3B implementation study)[4]. Teachers and other essential workers were offered Ad26.COV2.S from June 2021. BNT162.b2 vaccine was rolled out using an age-phased approach and by October 2021 vaccination was open to all individuals ≥ 18 years of age, with booster doses being introduced in November 2021[5−7]. National seroprevalence was estimated to be 98% by March 2022, indicating that the vast majority of South Africans had some protection against the SARS-CoV-2 virus, conferred by natural infection and/or vaccination[8].

COVID-19 vaccines have been shown to be safe and effective at preventing severe disease and death, however the majority of the available VE estimates are from high-income settings[9]. As of April 2023, data were available from 459 COVID-19 VE studies in 48 countries, with only 6 of these being from Africa[4, 10−15]. The generalizability of VE estimates from high-income settings to African populations is uncertain due to differences in vaccine products, accessibility and timing of vaccinations as well as underlying population differences. Studies from high-income settings reflect vaccines available in these settings, with fewer estimates available for adenovirus-vectored vaccines which are largely available in low- and middle-income countries[9]. Compared to many high-income settings, populations in Africa are younger and have a higher prevalence of underlying conditions such as TB and HIV, both factors likely to influence immune response and resulting protection[9]. South African data have demonstrated a higher risk of hospitalisation and death from SARS-CoV-2 infection amongst PLWH, highlighting this high-risk group as a priority for vaccination, especially since the HIV prevalence among 15−49 year olds in SA was estimated to be 19.5% in 2021[16−19]. Despite this, there are limited estimates for COVID-19 VE in PLWH, specifically in low resource settings.

In 2005 SA public sector employees across all departments and provinces were offered affordable medical insurance for themselves and their families. At the start of the current study period (May 2021) the scheme had 1 985 105 beneficiaries of which 757 222 were principal members. The aim of this study was to estimate VE against laboratory-confirmed COVID-19 hospitalisation, stratified by age group, time since vaccination and vaccine product for the three most recent SARS-CoV-2 surges (driven by the delta, omicron BA.1 and omicron BA.4/5 variants) among adults ≥ 18 years old (excluding HCWs) and among PLWH.

Methods

This analysis used a test-negative case-control study design with the outcome being hospitalisation for acute respiratory infection (ARI) among scheme members. Hospitalisations with a primary diagnosis (from hospital authorization diagnosis) of ARI including International Classification of Diseases (ICD10) codes J00 to J99 & U07, of any severity and duration, with a SARS-CoV-2 laboratory test (antigen or PCR) from a sample collected between 14 days prior to 3 days after the hospitalisation, were extracted from the scheme claims data. COVID-19 testing was identified using claims data for PCR tests and pathology laboratory data for PCR and antigen tests. Where information on date or result conflicted, laboratory data took precedence. Testing in claims data was identified using specialised COVID-19 tariff codes, industry standard PCR tariff codes with amount less than or equal to R850 (approximately $43, the regulated price for SARS-CoV-2 PCR tests in SA) and non-standard tariff codes that were accompanied by tariff descriptions indicated COVID-19 testing. Testing in pathology lab data was indicated by LOINC (logical observation identifiers, common names and codes). Cases were defined as hospitalisations with a diagnosis of ARI and a laboratory-confirmed positive SARS-CoV-2 test. Controls were defined as hospitalisations with a diagnosis of ARI and laboratory-confirmed negative SARS-CoV-2 test, with no laboratory-confirmed positive SARS-CoV-2 tests < 90 days prior to the hospitalisation. Subsequent hospitalisation matching the case or control definition after > 90 days was considered a new event.

Vaccination status was identified using National Pharmaceutical Product Interference (NAPPI) codes from claims data. Vaccines administered out of hospital were identified using claims data and in-hospital vaccines were identified using in-hospital NAPPI data as the related claim line data omits NAPPI codes. Individuals were considered fully vaccinated if the hospitalisation was ≥ 14 days after the second BNT162b2 dose or ≥ 28 days after first Ad26.COV2.S dose (primary series). Members were considered partially vaccinated if they received only one dose of BNT162b2 ≥ 14 days prior to the hospitalisation. Members were considered to have had a booster dose if they had received any vaccine dose in addition to the primary series with hospitalisation being ≥ 14 days after BNT162b2 booster dose and ≥ 28 days after Ad26.COV2.S booster dose. Individuals were considered unvaccinated if they had not received any COVID-19 vaccine prior to hospitalisation.

Only scheme members that were ≥ 18 years old at time of hospitalisation, with ≥ 1 year scheme membership prior to the start of the study period were included (to ensure data on comorbidities and vaccination were as accurate as possible). HCWs were excluded from the analysis since many were vaccinated through the Sisonke trial and hence vaccination information were not available through scheme claims data. In addition, HCWs have a unique risk profile which was less generalizable to the general South African population. Hospitalisation for those receiving vaccines other than BNT162b2 or Ad26.COV2.S were excluded from the analysis.

Comorbidities were identified by a combination of data sources as detailed in the supplementary information. HIV infection was identified based on registration with the Scheme's HIV management program. The program allows access to antiretroviral therapy (ART), monitoring and treatment of HIV.

Genomic sequencing was not available for hospitalisations among scheme members specifically, however proxy variant periods were defined as incidence > 30 cases per 100 000 population with each variant period being driven by a different variant as per national sequencing data (with the delta period from 9 May 2021 to 18 September 2021; omicron BA.1 from 28 November 2021 to 5 February 2022; and omicron BA.4/5 from 17 April 2022 to 28 May 2022)[20,21]. Hospitalisations outside of these periods were excluded. Total COVID-19 cases, hospitalisations and deaths per week for all scheme members was used to verify that this definition for proxy variant periods aligned with the scheme case data (Supplementary information, Figure S1).

Crude and adjusted logistic regression models were used to calculate the VE according to the formula VE=(1-OR)*100. Adjusted odds ratios (OR) were estimated by including the following variables a priori based on prior literature: age (18−49, 50−59, ≥ 60 years), presence or absence of comorbidities, documentation of previous SARS-CoV-2 infection (ever versus never) in the logistic regression model[22]. The following variables were investigated in the model but were not included as they did not significantly change the model: receipt of influenza vaccine (in the past year), receipt of PCV vaccine (in the past 5 years), sex, residence in a metropolitan area. The analysis was stratified by age group (18−49; 50−59; ≥60 years) and HIV-infection (infected or uninfected). Hospitalisation for partially vaccinated individuals were included as a separate group in the logistic regression model but estimates were not reported for this group. VE estimates were calculated separately for each vaccine product and by proxy variant period.

Results

A total of 16 826 hospitalisations meeting the definition of ARI diagnosis with a valid SARS-CoV-2 laboratory test during the proxy variant periods were included (Fig. 1). The proportion testing positive for SARS-CoV-2 was highest during the delta period (70.9%) and decreased with subsequent waves (63.5% during BA.1 and 41.5% during BA.4/5 period). The proportion unvaccinated was high during delta (94.1% of cases and 85.2% of controls), as this surge occurred early during the vaccine rollout, but decreased during BA.1 (43.7% of cases and 38.8% of controls) and BA.4/5 (35.3% of cases and 28.3% of controls). The number of hospitalisations having received booster doses was low for all three proxy variant periods (0, 8 and 291 individuals during delta, BA.1 and BA.4/5 respectively). These hospitalisations were excluded from further analysis as numbers were insufficient to calculate VE for booster doses.

Of the 16 527 hospitalisations included (excluding those with booster doses), 6669 (40.4%) were between the ages of 18−49, 4260 (25.8%) were 50−59 years old, 2638 (16.0%) were 60−69 years old and 2960 (17.9%) were 70 years or older (Table 1). Age distribution was similar by proxy variant period and cases were older than controls for all periods. The majority of hospitalisations were amongst females, with males making up 36.6% (6047) of overall hospitalisations which was similar by proxy variant period (37.7%, 35.9% and 31.4% males for delta, BA.1 and BA.4/5, respectively). Males made up a higher percentage of cases than controls overall and for all proxy variant periods, except during BA.4/5 when there was no significant difference between proportion of males in cases or controls (p = 0.247). The majority (59.7%) of hospitalisations were in individuals residing outside of the main metropolitan areas. Most hospitalisations (48.8%) were amongst individuals in the lowest income level (< R13000 per month). Only 3.7% (618) of hospitalisations had a previous documented SARS-CoV-2 infection with the proportion being significantly higher for controls than for cases throughout the variant periods (p < 0.001 for delta and BA.1 and p = 0.005 for BA.4/5). A higher proportion of cases compared to controls were unvaccinated for all proxy variant periods (94.1% versus 85.2%, p

< 0.001 for delta; 43.8% versus 38.8%, p = 0.003 for BA.1; 40.9% versus 32.9%, p < 0.001 for BA.4/5). Characteristics of included hospitalisations by SARS-CoV-2 vaccination status are provided in supplementary information (Table S1).

BNT162b2 showed a significantly protective VEs against COVID-19-related hospitalisation for all variant periods (89.3% (95% CI, 85.9−91.9) during the delta period, 31.4% (95% CI, 19.1−41.9) during the omicron BA.1 period and 22.7% (95% CI, 2.2−38.9) during the omicron BA.4/5 period) (Fig. 2). VE estimates for Ad26.COV2.S were also significantly protective against COVID-19-related hospitalisation for all proxy variant periods, however the estimates were lower than for BNT162b2 for delta and BA.1 (48.8% (95% CI, 39.6−56.5) and 19.8% (95% CI, 5.8−31.6)) and higher for BA.4/5 (45.0% (95% CI, 29.8−57.0)). Only estimates for vaccination < 3 months ago were calculated for delta period since delta was early during the vaccine rollout. When stratified by time since vaccination, BNT162b2 VE estimates during BA.1 remained significantly protective < 3 months, 3−5 months and ≥ 6 months since last vaccination (VE of 48.3% (95% CI, 29.8−61.9), 17.4% (95%, 0.2−31.7) and 62.1% (95% CI, 46.9−72.9) respectively). During BA.4/5 VE estimate remained significantly protective < 3 months since last vaccination (68.1% (95% CI, 24.3−86.8), however did not remain significantly protective 3−5 months or 6 + months after vaccination (14.6% (95% CI, -41.5-48.4) and 19.9% (95% CI, -3.1-37.7) respectively). For Ad26.COV2.S VE estimates were not significantly protective < 3 month or 3−5 months since vaccination during BA.1 or BA.4/5 (p = 0.345, p = 0.324, p = 0.053, p = 0.455 respectively). This is likely a result of small sample size for these time periods. Ad26.COV2.S was significantly protective after 6 months since last vaccination during BA.1 and BA.4/5 periods (53.0% (95% CI, 40.6−62.8) and 45.4% (95% CI, 29.7−57.5) respectively).

BNT162b2 conferred significant protection against COVID-19-related hospitalisation for 18−59 year olds and for ≥ 60 year olds during the delta period (88.9% (95% CI, 66.0-96.9) and 86.8% (95% CI, 82.4−90.1) respectively) and during the omicron BA.1 period (29.8% (95% CI, 11.4−44.4) and 32.9% (95% CI, 14.5−47.3) respectively; Fig. 3). During the omicron BA.4/5 period, BNT162b2 conferred significant protection against COVID-19-related hospitalisation in those over the age of 60 years (49.1% (95% CI, 26.3−65.0), however in the younger age group this protection was no longer significant (1.9% (95% CI, -35.0-5.3). Ad26.COV2.S conferred significant protection against COVID-19-related hospitalisation for those between 18−59 years during the delta period (50.5% (95% CI, 41.4−58.1)) and during the omicron BA.4/5 period (27.6% (95% CI, 5.3−44.7)), however VE was not significant during the omicron BA.1 period (12.0% (95% CI -4.8-26.2). In the older age group (≥ 60), VE was only significantly protective during the omicron BA.4/5 period (81.3% (95% CI, 57.1−91.9) and was not significant during the delta (-11.5% (95% CI, -227.5-62.1)) or omicron BA.1 periods (33.6% (95% CI, -9.6-59.7)).

BNT162b2 offered significant protection in HIV-uninfected individuals during all three proxy variant periods with the highest VE during delta (89.40%, 95% CI, 85.90−92.00), decreasing during BA.1 (32.20%, 95% CI, 19.30−43.10) and decreasing further during BA.4/5 (23.00%, 95% CI, 1.40−39.80) (Fig. 3). Amongst PLWH, BNT162b2 offered a significantly protective VE during delta which was comparable to the HIV-uninfected group (89.60%, 95% CI, 57.00-97.50), however the VE did not remain significant during the omicron variant periods. Ad26.COV2.S offered a significantly protective VE in HIV-uninfected individuals during delta (48.90%, 95% CI, 37.80−58.00) and a comparatively high VE during BA.4/5 (45.80%, 95% CI, 29.30−58.50). The VE during BA.1 was not significant. Amongst PLWH, Ad26.COV2.S offered a significantly protective VE during delta (42.50%, 95% CI, 21.80−57.70) and BA.1 (44.40%, 95% CI, 18.70−62.00), however the VE was not retained during BA.4/5 (29.10, 95% CI -37.20-63.40).

Discussion

Vaccination with either BNT162b2 or Ad26.COV.2 was protective against COVID-19-related hospitalisation during the delta, omicron BA.1 and omicron BA.4/5 proxy variant periods. The estimates for BNT162b2 were in line with those from South African medical insurance studies which estimated VEs of 93% (95% CI, 90−94)[23] during delta, 56.3% (95% CI, 51.6−60.5)[13] during BA.1 and 47.4% (95% CI, 19.9−65.5)[13] during BA.4/5 (compared to our estimates of 89% (95% CI, 86−92), 31% (95% CI, 19−42) and 23% (95% CI, 2−39) respectively). The VE estimate for Ad26.COV.2 during the proxy delta period of 49% (95% CI, 40−57) was slightly lower than for BNT162b2, although in a comparable range to the Sisonke study estimate of 62% (95% CI, 42−76)[4] during this same period. Although we did provide estimates stratified by time since vaccination, the study was underpowered to detect a clear pattern in VE over time. There was some evidence of waning for both BNT162b2 and Ad26.COV.2 during the BA.4/5 period.

BNT162b2 offered similar protection against COVID-19-related hospitalisation for 18−59 year olds and ≥ 60 year olds during both the delta and omicron BA.1 periods (89% (95% CI, 66−97) and 87% (95% CI, 82−90) during delta and 30% (95% CI, 11−44) and 33% (95% CI, 15−47) during BA.1). The estimates for BA4/5 period remained protective for the ≥ 60 year olds however were no longer protective for the 18−59 year olds. This could be due to an increase in incidental detection of SARS-CoV-2 amongst those admitted for other respiratory illnesses during the omicron period. The majority of individuals over the age of 60 years received BNT162b2 since Ad26.COV2.S was initially provided to HCWs, teachers and other essential workers. This study was therefore underpowered to estimate VE for ≥ 60 year olds during delta and omicron BA.1 periods for Ad26.COV2.S. Ad26.COV2.S did however provide significant protection against COVID-19-related hospitalisation for 18−59 year olds during delta (51% (95% CI, 41−58)) and omicron BA.4/5 periods (28% (95% CI, 5−45)).

The protection against COVID-19-related hospitalisation offered by both BNT162b2 and Ad26.COV.2S was comparable for PLWH and HIV-uninfected individuals for the three proxy variant periods, although there was an issue of small sample size in some groups, possibly resulting in some insignificant VE estimates. Studies in Canada reported VEs of 70% (95% CI 57−79%) against any infection and 61% (95% CI 6−84%) against symptomatic infection for BNT162b2 in PLWH and 71.1% (95% CI 39.1−86.1%) against symptomatic infection for BNT162b2, Moderna and ChAdOx1 combined[24,25]. These studies indicated a delayed VE peak and more rapid waning in PLWH when compared with HIV-uninfected individuals, however, vaccination was shown to be effective in protecting this high-risk group with peak VE estimates being comparable to estimates from HIV-uninfected individuals[24,25]. Data from SA HCWs estimated comparable VEs for a single dose of Ad26.COV2.S among PLWH and HIV-uninfected individuals, with estimates of 73% (95% CI 58−85%) and 65% (95% CI 13−93%) for hospitalisation and COVID-19-related death respectively during the first two variant periods.

Given the high underlying seroprevalence of COVID-19 antibodies in the South African population, this analysis estimates protection conferred by vaccination in addition to previous infection and should be interpreted as such. We were unable to estimate VE against infection or mild illness due to low testing rates

(49% of the scheme members had no documented record of COVID-19 test and only 19% had ever had a documented infection by June 2022) and changing testing policies. Unfortunately, we were unable to analyze VE by severity of HIV disease as data on HIV markers were not available. This is currently an important gap in available literature, with a lack of data specifically in those with advanced disease and an understanding of vaccine response in PLWH with a spectrum of disease, and should be the focus of future studies[26].

This analysis presents an evaluation of COVID-19 vaccines in a real public health program and is likely to reflect issues absent in clinical trial settings by including individual with a wider range of characteristics, varying dosing intervals, issues with vaccine storage and administration[9]. We believe that the data are representative of the SA population since the scheme insures clients nationwide, from an array of backgrounds and income levels. Despite this, the unemployed and the poorest in the population are excluded from these estimates.

The World Health Organization (WHO) recently updated recommendations for the use of COVID-19 vaccines in the context of omicron and population seroprevalence[27]. These recommendations highlight older adults and those with significant comorbidities (including HIV) as high-risk individuals that should be prioritized for primary series and additional booster doses. Data presented here indicate that vaccination offers significant protection in PLWH and adults over the age of 60 years (comparable to HIV-uninfected and 18–59 year olds respectively) and therefore is an effective means of reducing severe outcomes in these high-risk populations in South Africa.

Declarations

Ethics approval

This study was approved by the University of the Witwatersrand, Human Research Ethics Committee (HREC) (ethics reference number: 211110).

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Acknowledgments

Data availability

Data are personal, medical insurance data and are therefore not publically available.

Conflict of interest

None to declare.

Authors' contributions

SLJ, DS, NC, LM, CC, MJG conceptualized and designed the study. SLJ, DS, NC, LM, CW, JB-H, SM, CG, BM, MS, CC, MJG acquired, analysed and interpreted the data. SLJ drafted the work. CW, SM, MS, BM, CC, MJG Substantively revised the work. All authors read and approved the final manuscript.

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Tables

Table 1: Characteristics of cases and controls by proxy variant period

	Overall				Delta				Omicron BA.1			
	Total (16527)	Controls (5643)	Cases (10884)	p^a	Total (10627)	Controls (3095)	Cases (7532)	p^a	Total (4090)	Controls (1491)	Cases (2599)	p
Age group [b], years 18-49 (n; %)	6669; 40.4	2929; 51.9	3740; 34.4	<0.001	4052; 38.1	1651; 53.3	2401; 31.9	<0.001	1735; 42.4	713; 47.8	1022; 39.3	<
50-59 (n; %)	4260; 25.8	1232; 21.8	3028; 27.8		3073; 28.9	679; 21.9	2394; 31.8		837; 20.5	320; 21.5	517; 19.9	
60-69 (n; %)	2638; 16.0	725; 12.9	1913; 17.6		1744; 16.4	374; 12.08	1370; 18.2		657; 16.1	216; 14.5	441; 17.0	
70+ (n; %)	2960; 17.9	757; 13.4	2203; 20.2		1758; 16.5	391; 12.6	1367; 18.2		861; 21.1	242; 16.2	619; 23.8	
Male sex (n; %)	6047; 36.6	1922; 34.0	4125; 37.9	<0.001	4008; 37.7	1074; 34.7	2934; 39.0	<0.001	1470; 35.9	553; 37.1	917; 35.3	0
Residence in metro [c] (n; %)	6654; 40.3	2197; 38.9	4457; 41.0	0.012	4212; 39.6	1186; 38.3	3026; 40.2	0.076	1664; 40.7	597; 40.0	1067; 41.1	0
Income level [d] Lowest (n; %)	8069; 48.8	2575; 45.6	5494; 50.5	<0.001	5176; 48.7	1396; 45.1	3780; 50.2	<0.001	2061; 50.4	720; 48.3	1341; 51.6	0
Low (n; %)	2174; 13.2	880; 15.6	1294; 11.9		1315; 12.4	487; 15.7	828; 11.0		583; 14.3	232; 15.6	351; 13.5	
Middle (n; %)	3174; 19.2	1158; 20.5	2016; 18.5		2079; 19.6	642; 20.7	1437; 19.1		729; 17.8	279; 18.7	450; 17.3	
Upper (n; %)	3110; 18.8	1030; 18.3	2080; 19.1		2057; 19.4	570; 18.4	1487; 19.7		717; 17.5	260; 17.4	457; 17.6	
Employment department [e] Education (n; %)	4429; 26.8	1688; 29.9	2741; 25.2	<0.001	2934; 27.6	937; 30.3	1997; 26.5	<0.001	985; 24.1	405; 27.2	580; 22.3	<
Police services (n; %)	398; 2.4	146; 2.6	252; 2.3		247; 2.3	79; 2.6	168; 2.2		108; 2.6	45; 3.0	63; 2.4	
Correctional services (n; %)	606; 3.7	187; 3.3	419; 3.9		411; 3.9	114; 3.7	297; 3.9		138; 3.4	41; 2.8	97; 3.7	
Pensioners (n; %)	2402; 14.5	626; 11.1	1776; 16.3		1565; 14.7	344; 11.1	1221; 16.2		632; 15.5	187; 12.5	445; 17.1	
Other (n; %)	8692; 52.6	2996; 53.1	5696; 52.3		5470; 51.5	1621; 52.4	3849; 51.1		2227; 54.5	813; 54.5	1414; 54.4	
Previous documented SARS-CoV-2 infection [f] (n; %)	618; 3.7	398; 7.1	220; 2.0	<0.001	346; 3.3	227; 7.3	119; 1.6	<0.001	181; 4.4	105; 7.0	76; 2.9	<
Co-morbidities [g] Chronic lung disease; excluding TB (n; %)	4538; 27.5	1934; 34.3	2604; 23.9	<0.001	3006; 28.3	1029; 33.2	1977; 26.3	<0.001	998; 24.4	529; 35.5	469; 18.1	<
Diabetes mellitus (n; %)	4067; 24.6	983; 17.4	3084; 28.3	<0.001	2745; 25.8	530; 17.1	2215; 26.4	<0.001	975; 23.8	269; 18.0	706; 27.2	<
Blood disorders (n; %)	966; 5.8	371; 6.6	595; 5.5	0.004	551; 5.2	190; 6.1	361; 4.8	0.004	306; 7.5	115; 7.7	191; 7.4	0
Cardiovascular disease (n; %)	1441; 8.7	427; 7.6	1014; 9.3	<0.001	922; 8.7	249; 8.1	673; 8.9	0.139	381; 9.3	114; 7.7	267; 10.3	0
Hypertension (n; %)	7760; 47.0	2103; 37.3	5657; 52.0	<0.001	5186; 48.8	1140; 36.8	4046; 53.7	<0.001	1834; 44.8	572; 38.4	1262; 48.6	<
Neurological disorder (n; %)	578; 3.5	169; 3.0	409; 3.8	0.011	357; 3.4	94; 3.0	263; 3.5	0.237	161; 3.9	47; 3.2	114; 4.4	0
Guillain Barre Syndrome (n; %)	1; 0.0	0; 0.0	1; 0.0	>0.99	1; 0.0	0; 0.0	1; 0.0	>0.99	0; 0.0	0; 0.0	0; 0.00	-
Immunocompromised; excluding HIV (n; %)	119; 0.7	39; 0.7	80; 0.7	0.752	65; 0.6	21; 0.7	44; 0.6	0.571	42; 1.0	11; 0.7	31; 1.2	0
Renal disease (n; %)	400;	86; 1.5	314; 2.9	<0.001	242; 2.3	49; 1.6	193;	0.002	128;	26; 1.7	102;	<

	2.4						2.6	3.1		3.9	
GI/Liver disease (n; %)	86; 0.5	29; 0.5	57; 0.5	0.934	51; 0.5	15; 0.5	36; 0.5	0.964	21; 0.5	6; 0.4	15; 0.6
Rheumatologic/autoimmune (n; %)	594; 3.6	162; 2.9	432; 4.0	<0.001	378; 3.6	93; 3.0	285; 3.8	0.049	156; 3.8	39; 2.6	117; 4.50
HIV (n; %)	2189; 13.2	895; 15.9	1294; 11.9	<0.001	1384; 13.0	495; 16.0	889; 11.8	<0.001	560; 13.7	215; 14.4	345; 13.3
TB (n; %)	34; 0.2	25; 0.4	9; 0.1	<0.001	20; 0.2	18; 0.6	2; 0.0	<0.001	13; 0.3	7; 0.5	6; 0.23
Any co-morbidity [h] (n; %)	11993; 72.6	3917; 69.4	8076; 74.2	<0.001	7861; 74.0	2124; 68.6	5737; 76.2	<0.001	2895; 70.8	1053; 70.6	1842; 70.9
Received influenza vaccine in the year before admission (n; %)	1381; 8.4	456; 8.1	925; 8.5	0.357	904; 8.5	247; 8.0	657; 8.7	0.213	381; 9.3	153; 10.3	228; 8.8
Received pneumococcal vaccine in the 5 years before admission (n; %)	60; 0.4	27; 0.5	33; 0.3	0.076	37; 0.4	14; 0.5	23; 0.3	0.243	17; 0.4	9; 0.6	8; 0.3
SARS-CoV-2 vaccination status Unvaccinated (n; %)	12100; 73.2	3565; 63.2	8535; 78.4	<0.001	9728; 91.5	2638; 85.2	7090; 94.1	<0.001	1716; 42.0	579; 38.8	1137; 43.8
Primary BNT162b2 series [i] (n; %)	2144; 13.0	964; 17.1	1180; 10.8		237; 2.2	154; 5.0	83; 1.1		1295; 31.7	479; 32.1	816; 31.4
Primary AD26.COV2.S series (n; %)	2283; 13.8	1114; 19.7	1169; 10.7		662; 6.2	303; 9.8	359; 4.8		1079; 26.4	433; 29.0	646; 24.9
Time since last vaccination [j] <3 months (n; %)	1207; 7.3	620; 11.0	587; 5.4	<0.001	898; 8.5	456; 14.7	442; 5.9	<0.001	268; 6.6	132; 8.9	136; 5.2
3-5 months (n; %)	1685; 10.2	575; 10.2	1110; 10.2		1; 0.0	1; 0.0	0; 0.0		1575; 38.5	507; 34.0	1068; 41.1
6+ months (n; %)	1535; 9.3	883; 15.7	652; 6.0		0; 0.0	0; 0.0	0; 0.0		531; 13.0	273; 18.3	258; 9.9

[a] p-values generated by chi-squared test comparing cases and controls for the separate variant periods and the variant periods combined for each variable; [b] age group at the time of admission, [c] Defined as residence in one of eight urbanized, metropolitan areas (Buffalo City, City of Cape Town, Ekurhuleni Metropolitan Municipality, City of eThekwini, City of Johannesburg, Mangaung Municipality, Nelson Mandela Metropolitan Municipality, and the City of Tshwane); [d] income level of main member based on employment package (categorized as per Department of Public Service and Administration monthly income categories: lowest = <R13 000, low = R13 000 – R18 000, middle = R18 000 –R23 000, high = >R23 000); [e] employment department (with dependents defined as per main member, including education, police services, correctional services and pensioners, with all remaining departments grouped as 'other'); [f] documented SARS-CoV-2 laboratory confirmed infection >90 days of admission (positive tests within 90 days of each other were considered to be the same episode), [g] specific comorbidities (sub-conditions matched to GEMS chronic medicine registration, primary diagnosis for episode of care, hospital authorization and tariff code for appliances and grouped into chronic conditions as per detailed spreadsheet); [h] presence of any of the specified co-morbidities; [i] all individuals receiving two BNT162b2 doses received the second dose ≥28 days after the first; [j] time since last vaccination date to admission date.

Figures

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                    16 826 admissions
                    with ARI diagnosis and
                    SARS-CoV-2 test
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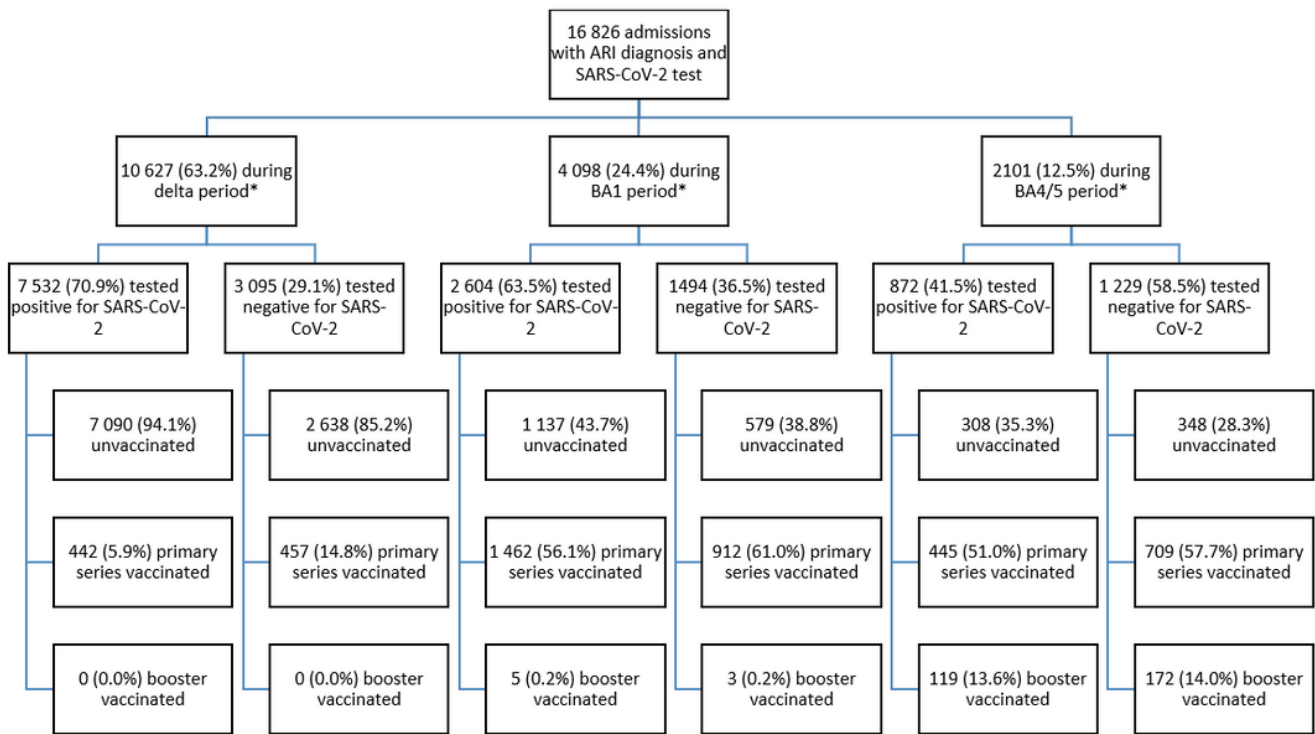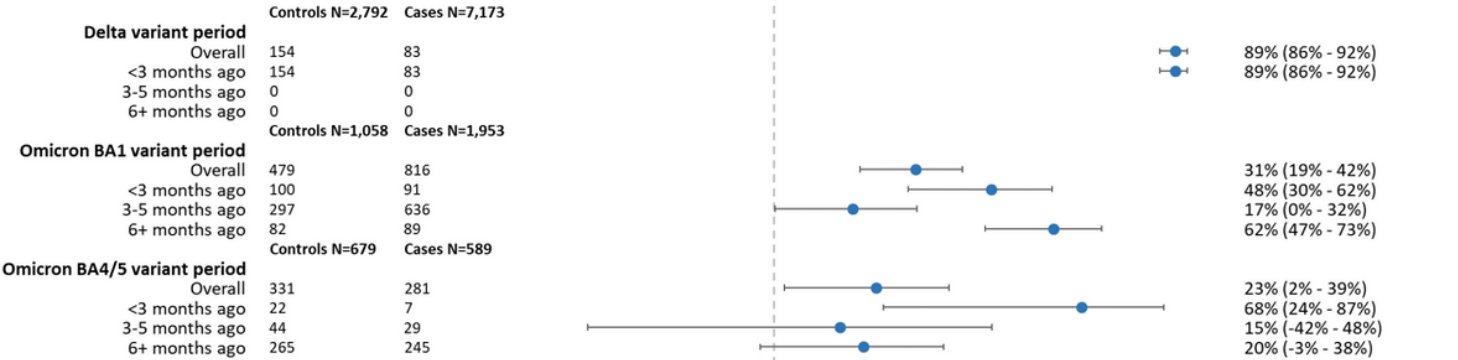| 10 627 (63.2%) during delta period*		4 098 (24.4%) during BA1 period*		2101 (12.5%) during BA4/5 period*	
7 532 (70.9%) tested positive for SARS-CoV-2	3 095 (29.1%) tested negative for SARS-CoV-2	2 604 (63.5%) tested positive for SARS-CoV-2	1494 (36.5%) tested negative for SARS-CoV-2	872 (41.5%) tested positive for SARS-CoV-2	1 229 (58.5%) tested negative for SARS-CoV-2
7 090 (94.1%) unvaccinated	2 638 (85.2%) unvaccinated	1 137 (43.7%) unvaccinated	579 (38.8%) unvaccinated	308 (35.3%) unvaccinated	348 (28.3%) unvaccinated
442 (5.9%) primary series vaccinated	457 (14.8%) primary series vaccinated	1 462 (56.1%) primary series vaccinated	912 (61.0%) primary series vaccinated	445 (51.0%) primary series vaccinated	709 (57.7%) primary series vaccinated
0 (0.0%) booster vaccinated	0 (0.0%) booster vaccinated	5 (0.2%) booster vaccinated	3 (0.2%) booster vaccinated	119 (13.6%) booster vaccinated	172 (14.0%) booster vaccinated

Figure 1

Flow diagram indicating hospitalisations included in the analysis

*Only hospitalisations during the variant periods (delta period from 9 May 2021 to 18 September 2021; omicron BA.1 from 28 November 2021 to 5 February 2022; and omicron BA.4/5 from 17 April 2022 to 28 May 2022) were included.

BNT162b2 Primary Series   **Adjusted VE (95%CI)**

	Controls N=2,792	Cases N=7,173		Adjusted VE (95%CI)
Delta variant period				
Overall	154	83		89% (86% - 92%)
<3 months ago	154	83		89% (86% - 92%)
3-5 months ago	0	0		
6+ months ago	0	0		
	Controls N=1,058	Cases N=1,953		
Omicron BA1 variant period				
Overall	479	816		31% (19% - 42%)
<3 months ago	100	91		48% (30% - 62%)
3-5 months ago	297	636		17% (0% - 32%)
6+ months ago	82	89		62% (47% - 73%)
	Controls N=679	Cases N=589		
Omicron BA4/5 variant period				
Overall	331	281		23% (2% - 39%)
<3 months ago	22	7		68% (24% - 87%)
3-5 months ago	44	29		15% (-42% - 48%)
6+ months ago	265	245		20% (-3% - 38%)

Ad.COV2.S Primary Series   **Adjusted VE (95%CI)**

	Controls N=2,941	Cases N=7,449		Adjusted VE (95%CI)
Delta variant period				
Overall	303	359		49% (40% - 57%)
<3 months ago	302	359		49% (40% - 56%)
3-5 months ago	1	0		
6+ months ago	0	0		
	Controls N=1,012	Cases N=1,783		
Omicron BA1 variant period				
Overall	433	646		20% (6% - 32%)
<3 months ago	32	45		20% (-28% - 50%)
3-5 months ago	210	432		-10% (-34% - 9%)
6+ months ago	191	169		
	Controls N=726	Cases N=472		
Omicron BA4/5 variant period				
Overall	378	164		45% (30% - 57%)
<3 months ago	10	2		78% (-2% - 95%)
3-5 months ago	23	13		24% (-55% - 63%)
6+ months ago	345	149		45% (30% - 58%)

Vaccine effectiveness (%) ± 95%CI
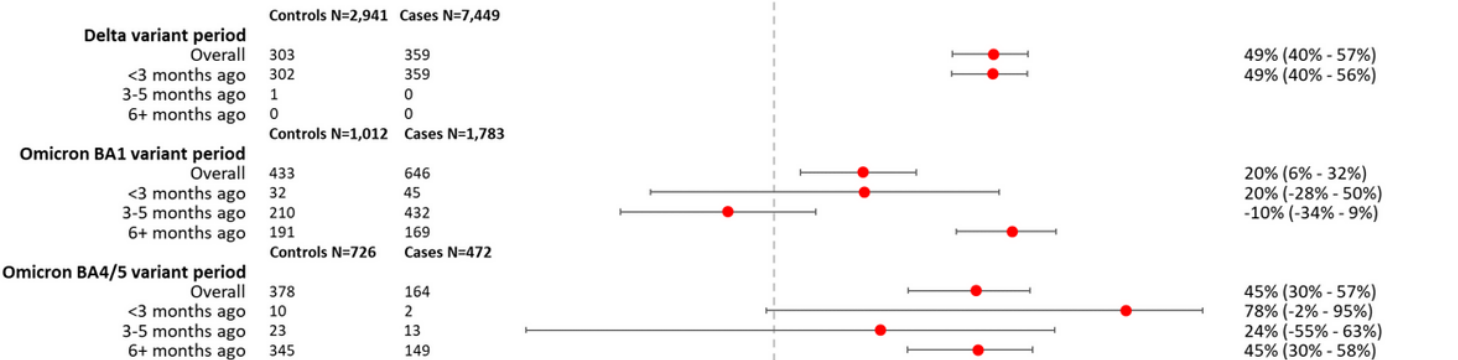
-130   -80   -30   20   70

Figure 2

VE against COVID-19-related hospitalisation amongst GEMS members for three variant periods

*Adjusted for age (18-49, 50-59, ≥60 years), presence of comorbidities and documented previous SARS-CoV-2 infection (ever versus never)

BNT162b2 Primary Series

	Controls	Cases	Adjusted VE (95%CI)
18 to 59 years			
Delta variant period	11/2031	3/4456	89% (66% - 97%)
Omicron BA1 variant period	181/628	208/947	30% (11% - 44%)
Omicron BA4/5 variant period	155/443	95/279	2% (-35% - 29%)
60+ years			
Delta variant period	143/761	80/2717	87% (82% - 90%)
Omicron BA1 variant period	298/430	608/1006	33% (15% - 47%)
Omicron BA4/5 variant period	176/236	186/310	49% (26% - 65%)
HIV negative			
Delta variant period	148/2391	80/6392	89% (86% - 92%)
Omicron BA1 variant period	447/956	755/1743	32% (19% - 43%)
Omicron BA4/5 variant period	293/586	269/555	23% (1% - 40%)
People living with HIV			
Delta variant period	6/401	3/781	90% (57% - 98%)
Omicron BA1 variant period	32/102	61/210	19% (-38% - 53%)
Omicron BA4/5 variant period	38/93	12/34	31% (-62% - 71%)

Ad.COV2.S Primary Series

	Controls	Cases	Adjusted VE (95%CI)
18 to 59 years			
Delta variant period	299/2319	339/4792	51% (41% - 58%)
Omicron BA1 variant period	405/852	592/1331	12% (-5% - 26%)
Omicron BA4/5 variant period	355/643	155/339	28% (5% - 45%)
60+ years			
Delta variant period	4/622	20/2657	-12% (-228% - 62%)
Omicron BA1 variant period	28/160	54/452	34% (-10% - 60%)
Omicron BA4/5 variant period	23/83	9/133	81% (57% - 92%)
HIV negative			
Delta variant period	209/2452	251/6563	49% (38% - 58%)
Omicron BA1 variant period	320/829	511/1499	12% (-5% - 27%)
Omicron BA4/5 variant period	286/579	138/424	46% (29% - 59%)
People living with HIV			
Delta variant period	94/489	108/886	43% (22% - 58%)
Omicron BA1 variant period	113/183	135/284	44% (19% - 62%)
Omicron BA4/5 variant period	92/147	26/48	29% (-37% - 63%)

Vaccine effectiveness (%) ± 95%CI

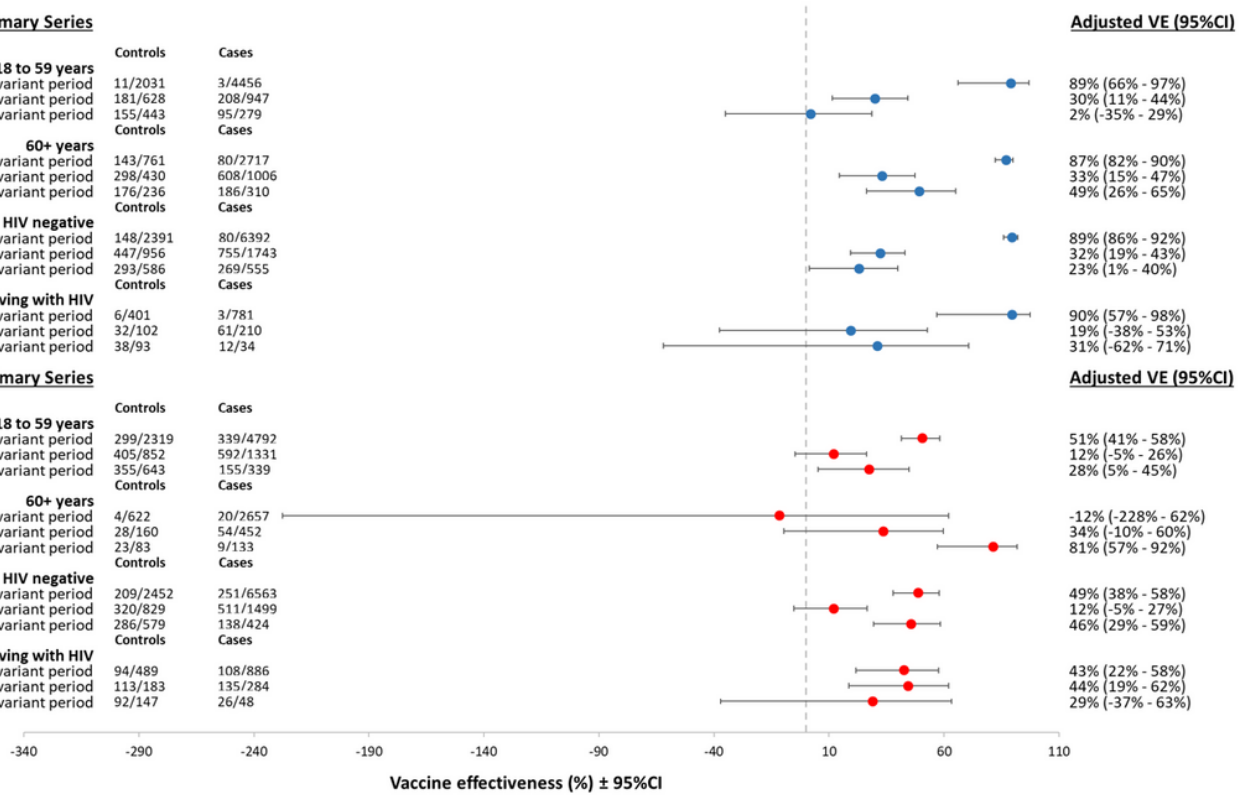(x-axis: -340, -290, -240, -190, -140, -90, -40, 10, 60, 110)

Figure 3

VE against COVID-19-related hospitalisation amongst GEMS members for three variant periods, stratified by age and by HIV status

*Adjusted for presence of comorbidities other than HIV, age group (18-49; 50-59; 60+), documentation of previous SARS-CoV-2 infection (ever versus never) in multivariate analysis

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryinformation.docx