

COVID-19 vaccine uptake and effectiveness by time since vaccination in the Western Cape province, South Africa: An observational cohort study during 2020-2022

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Abstract

Background

There are few data on the real-world effectiveness of COVID-19 vaccines and boosting in Africa, which experienced high levels of SARS-CoV-2 infection in a mostly vaccine-naïve population, and has limited vaccine coverage and competing health service priorities. We assessed the association between vaccination and severe COVID-19 in the Western Cape, South Africa.

Methods

We performed an observational cohort study of >2 million adults during 2020-2022. We described SARS-CoV-2 testing, COVID-19 outcomes, and vaccine uptake over time. We used multivariable cox models to estimate the association of BNT162b2 and Ad26.COV2.S vaccination with COVID-19-related hospitalisation and death, adjusting for demographic characteristics, underlying health conditions, socioeconomic status proxies and healthcare utilisation.

Results

By end 2022, only 41% of surviving adults had completed vaccination and 8% a booster dose, despite several waves of severe COVID-19. Recent vaccination was associated with notable reductions in severe COVID-19 during distinct analysis periods dominated by Delta, Omicron BA.1/2 and BA.4/5 (sub)lineages: within 6 months of completing vaccination or boosting, vaccine effectiveness was 46-92% for death (range across periods), 45-92% for admission with severe disease or death, and 25-90% for any admission or death. During the Omicron BA.4/5 wave, within 3 months of vaccination or boosting, BNT162b2 and Ad26.COV2.S were each 84% effective against death (95% CIs: 57-94 and 49-95, respectively). However, there were distinct reductions of VE at larger times post completing or boosting vaccination.

Conclusions

Continued emphasis on regular COVID-19 vaccination including boosting is important for those at high risk of severe COVID-19 even in settings with widespread infection-induced immunity.

Key words

COVID-19, SARS-CoV-2, vaccine effectiveness, South Africa, cohort, observational

Introduction

Globally we have transitioned from emergency to long-term management of COVID-19 with reduced COVID-19 severity and high levels of population immunity from both prior infection and vaccination.¹ A key component of long-term management is optimizing vaccination strategies to protect those at high risk of severe COVID-19 as protection conferred by infection or vaccination against severe disease may wane²⁻⁴ and there remains uncertainty about future SARS-CoV-2 evolution. However, the value of continued provision of vaccination opportunities is unclear in Africa and low- and middle-income countries (LMICs) where there were high levels of infection before vaccination became available;^{5,6} achieving primary vaccine and especially booster uptake has been challenging;⁷ and there are competing health service priorities such as HIV and tuberculosis, many of which were adversely affected during the COVID-19 pandemic.⁸⁻¹¹ While most of those vaccinated in LMICs are likely to have hybrid immunity (prior infection and vaccination)^{5,6} which has been shown to provide the most durable protection against severe disease in high-income country studies, there are few studies of long-term vaccine effectiveness in the context of very high levels of infection before vaccine availability, as experienced in countries such as South Africa (SA).² While a health insurance scheme in SA showed rapid waning of protection of BNT162b2 vaccination against severe disease, with restoration by booster vaccination, applicability to the uninsured, poorer population is unclear.¹² Uninsured persons likely have higher levels of prior infection than the insured and a different comorbidity burden, and are more similar to populations from other LMICs. Real-world data on durability of vaccine protection in these populations are needed to assess the benefit of ongoing COVID-19 vaccination in these contexts.

By merging multiple data sources curated by the Western Cape Government Department of Health and Wellness (WCGHW), we studied the association of COVID-19 vaccination with three COVID-19 hospitalisation and death outcomes amongst >2 million adult public sector healthcare users in the Western Cape (WC) province of SA. We studied this association over time (from vaccine rollout through three subsequent COVID-19 waves through end 2022); and differentiated vaccine state by type of vaccine (Ad26.COV2.S or BNT162b2), completeness of primary vaccination, and time in the vaccine state. The WCGHW regularly shared latest results from this study with advisory groups to inform the provincial and national vaccination program.

Methods

Study population, study period, and data sources

We studied adult (aged ≥ 18 years) public sector healthcare users (≥ 1 public sector healthcare encounter in the five years preceding 1 March 2020, the start of the COVID-19 pandemic) in the WC, who had a civil identification number enabling linkage to the national death registry. We excluded persons vaccinated before 17 May 2021, as earlier vaccination was restricted to healthcare workers.

The Western Cape Provincial Health Data Centre (PHDC) compiles de-identified person-level longitudinal data by integrating patient data from multiple information systems (administrative, laboratory, pharmacy, hospital and disease management) in all public sector health facilities in the province.¹³ These data are used to infer various health conditions, with estimated onset dates. Additionally, for this analysis, the dates and types of administered COVID-19 vaccines were obtained from the national Electronic Vaccine Data System (EVDS).¹⁴ Data on all positive and negative SARS-

CoV-2 PCR and antigen tests were obtained from public or private laboratories, or from consolidated laboratory data assembled by the National Institute for Communicable Diseases (NICD).¹⁵ PHDC public sector hospital data were supplemented by data on private sector COVID-19 admissions from the NICD hospital surveillance system (DATCOV).^{16,17} Data were linked to the national vital registration system to complete ascertainment of mortality.^{18,19}

Data were extracted during February 2023 after which SA has not experienced substantial surges in documented SARS-CoV-2 infections. The cohort was studied from 1 Jan 2020 until 31 Dec 2022, to allow for delays in outcome ascertainment. During this period, SA experienced five distinct COVID-19 waves with a different SARS-CoV-2 (sub)lineage dominating in each. For this study, each ‘wave’ period began when the dominant virus (sub)lineage first accounted for $\geq 20\%$ of the week’s sequenced specimens nationally, and continued until the next wave. The five wave periods, derived in **Appendix A1**, correspond to the Ancestral (starting 1 Mar 2020), Beta (18 Oct 2020), Delta (30 May 2021), Omicron BA.1 or BA.2 (14 Nov 2021), and Omicron BA.4 or BA.5 (3 Apr 2022–2 Jul 2022) (sub)lineages.

The study was approved by the University of Cape Town Health Research Ethics Committee (HREC REF 460/2020) and WCGHW. Individual informed consent requirement was waived for this analysis of de-identified data.

Definition of outcomes

We aimed to study severe COVID-19 and defined three COVID-19 outcomes, with each successive outcome (as ordered below) using a stricter definition of ‘severe’ disease, noting that some patients who died from COVID-19 were not hospitalised. Our outcomes were SARS-CoV-2 diagnoses associated with COVID-19 related (1) hospital admission (with disease of any severity), or death; (2) hospital admission with severe disease (i.e., requiring an intensive care unit or steroid prescription), or death; and (3) death alone. An admission or death was deemed COVID-19 related if sufficiently close to the SARS-CoV-2 diagnosis date, with no record of non-natural causes – see definitions in **Appendix A2**. SARS-CoV-2 testing was extremely limited in SA: seroprevalence studies suggest approximately 1 in 10 infections were diagnosed,⁶ and there was negligible use of self-tests during the study period. Therefore, ‘any SARS-CoV-2 diagnosis’ was not studied as an outcome.

Definition of vaccine states

Vaccines became available to the general population on 17 May 2021, with the minimum eligibility age progressively reducing from 60 years to 12 years by 20 October 2021. As the primary vaccination series, persons either received the single-dose Janssen Ad26.COV2.S or two-dose Pfizer-BioNTech BNT162b2 vaccine, though immunocompromised individuals were eligible for an additional homologous vaccine dose. From January 2022, all adults could receive additional booster doses 180 days after last doses.

In the analyses, persons could move through different vaccine states over time, from being ‘unvaccinated’, briefly into a ‘transition’ state (<28 days after Ad26.COV2S or <21 days after BNT162b2) immediately after receiving their first dose of any vaccine, and then among three vaccinated states. At any time, a vaccinated person could have received a ‘Complete Ad26.COV2S’ (≥ 28 days after single dose), ‘Incomplete BNT162b2’ (no second dose, or <14 days thereafter) or ‘Complete

BNT162b2' (≥ 14 days after second dose) vaccination series. Among those with complete vaccination, we did not explicitly disaggregate by number of boosters due to limited booster uptake, and instead distinguished by 'time in state' (<3, 3-5, 6-8 and ≥ 9 months): this time started increasing from zero upon entering the vaccine state, and restarted (from zero) seven days after any booster dose. See **Appendix A3** for detailed definitions. We considered only the type of the first vaccine, as very few persons received heterologous doses.

Statistical methods

We described over time the rate of each COVID-19 outcome, as well as the proportions of: those people with a documented SARS-CoV-2 infection who experienced each COVID-19 outcome, SARS-CoV-2 tests that were positive, and people in each vaccine state.

To estimate the association of vaccination with each outcome, we used a cox proportional hazards model with time-varying vaccine terms (vaccine state and time in state) and covariates, and parameterized it to allow the outcome rate to vary with calendar time. In SA, by definition, persons could not acquire a new SARS-CoV-2 infection within 90 days of the start of a previous documented infection, and were therefore removed from the at-risk population during these periods. People were censored at deaths that were not COVID-19 related. 'Vaccine effectiveness' (VE) was defined as one minus the model-estimated hazard ratio describing the rate of the outcome in a chosen vaccinated state versus in the reference unvaccinated state.

We adjusted for several covariates, and continuous covariates were categorised *a priori*. Demographic characteristics were sex and (time-varying) age. Time-varying health conditions were diabetes, hypertension, chronic kidney disease, chronic respiratory disease, HIV, 'any' tuberculosis (previous or ongoing), an 'ongoing' tuberculosis episode, pregnancy and a prior SARS-CoV-2 diagnosis. Location (subdistrict/district) and location type for the most recent primary healthcare facility visit (within Cape Town Metro, versus non-Metro or no recorded visit) were potential measures of socioeconomic status and healthcare access. The number (total for 5 years) and regularity (number of years with visits in 3 years) of primary healthcare facility visits before the pandemic (March 2020), and the number of negative SARS-CoV-2 tests more than 90 days before each analysis period (defined below), acted as proxies for other health risks and service use. All covariates were entered as main effects, though we used a likelihood ratio test (LRT) to investigate modification of VE by HIV status. **Appendix A4** contains detailed definitions of covariates.

Given the complexity of the evolving virus, setting and study population, we expected associations of COVID-19 outcomes with vaccination and covariates to change over our study period. We therefore fitted separate models to each of the analysis wave periods (defined above) from vaccine rollout, interpreting each estimated VE as an average VE over that period.

As supplementary analyses, we examined VE for distinct subpopulations based on sex, age and HIV status at start 2020, and when excluding people who received heterologous doses. We also estimated VE over short 6-week rolling windows of time.

Results

Description of cohort characteristics, vaccination and COVID-19 outcomes

Among 2,429,927 WC adult public sector healthcare users at start 2020, median age was 38 years (inter-quartile range: 28,52), and 60% were female (**Table 1**). There was a high burden of inferred non-communicable conditions (end 2022: 23% and 10% had hypertension and diabetes, respectively; 8% and 4% had chronic respiratory disease and chronic kidney disease) and inferred infectious conditions (15% and 10% were living with HIV and had ever experienced tuberculosis).

Only 40% of the cohort studied from 2020 was completely vaccinated by end 2022 (**Table 2**), and 8% received a booster. Heterologous doses were received by only 28 persons during primary vaccination, and by <1.5% of vaccinated persons during boosting. About 1 in 200 experienced COVID-19 related death; 1 in 150 COVID-19 related hospitalisation with severe disease, or death; and 1 in 60 COVID-19 related hospitalisation, or death. 21% of COVID-19 related deaths occurred without a COVID-19 related hospitalisation.

During the five COVID-19 waves of 2020-2022, weekly SARS-CoV-2 diagnoses reached a highest peak of 17 per 100 person years and test positivity reached 54%; with high overall mortality (6%) in those with documented SARS-COV-2 infection (**Figure 1A-1C**). Vaccines were available from mid-2021. By start 2022, 38% of the surviving cohort were completely vaccinated, with limited further vaccine uptake (**Figure 1D**). By end 2022, 5% of the surviving cohort had an incomplete vaccination series; and 41% had a complete series (71% BNT162b2), of whom only 3% completed or boosted vaccination within the last 6 months.

Comparing vaccination over time by age group (**Figure 2**), vaccine uptake was highest in the oldest persons (end 2022: 33% and 51% completely vaccinated among 18-34 and ≥ 60 -year-old persons, respectively). During the Omicron periods (end 2021 through 2022), completion of vaccination series and booster uptake was also highest in oldest persons (end 2022: 4% and 19% with boosters in 18-34 and ≥ 60 -year-olds, respectively).

See **Appendix B1** for tables of all analysis variables, including by age group; and **Appendix B2** for plots of outcomes, testing and vaccination over time, by sex, age group and HIV status.

Table 1: Demographic characteristics and non-communicable and infectious conditions in the cohort of South African adults utilising public sector healthcare in the Western Cape province, studied during calendar years 2020 through 2022, also stratified by completion of a primary COVID-19 vaccination series by end 2022. Percent (count frequency) is reported.

Characteristics and conditions (2020-2022)	Overall N = 2,429,927	Complete vaccination by end 2022 ^a	
		No N = 1,455,385	Yes N = 974,542
Age category at start 2020 (years)			
18-34	41.6 (1,009,672)	46.6 (677,813)	34.1 (331,859)
35-49	29.3 (711,077)	27.2 (395,497)	32.4 (315,580)
50-59	14.1 (342,308)	12.4 (179,961)	16.7 (162,347)
60+	15.1 (366,870)	13.9 (202,114)	16.9 (164,756)
Sex			
Female	59.7 (1,450,660)	57.8 (841,578)	62.5 (609,082)
Male	40.3 (979,267)	42.2 (613,807)	37.5 (365,460)
Hypertension			
Absent at end 2022	76.5 (1,858,079)	79.8 (1,161,884)	71.4 (696,195)
Onset during 2020-2022	3.4 (83,174)	2.8 (40,473)	4.4 (42,701)
Present before 2020	20.1 (488,674)	17.4 (253,028)	24.2 (235,646)
Diabetes			
Absent at end 2022	89.5 (2,174,691)	90.8 (1,321,701)	87.5 (852,990)
Onset during 2020-2022	1.9 (46,111)	1.6 (22,634)	2.4 (23,477)
Present before 2020	8.6 (209,125)	7.6 (111,050)	10.1 (98,075)
Chronic kidney disease			
Absent at end 2022	95.7 (2,324,768)	95.9 (1,396,419)	95.3 (928,349)
Onset during 2020-2022	0.7 (16,445)	0.5 (7,707)	0.9 (8,738)
Present before 2020	3.7 (88,714)	3.5 (51,259)	3.8 (37,455)
Chronic respiratory disease			
Absent at end 2022	92.2 (2,241,094)	92.5 (1,346,451)	91.8 (894,643)
Onset during 2020-2022	1.5 (36,451)	1.4 (20,454)	1.6 (15,997)
Present before 2020	6.3 (152,382)	6.1 (88,480)	6.6 (63,902)
HIV			
Absent at end 2022	85.4 (2,075,796)	85.3 (1,241,925)	85.6 (833,871)
Onset during 2020-2022	1.4 (32,986)	1.4 (21,048)	1.2 (11,938)
Present before 2020	13.2 (321,145)	13.2 (192,412)	13.2 (128,733)
Tuberculosis (at any time in past)^b			
Absent at end 2022	90.2 (2,190,920)	89.2 (1,298,552)	91.6 (892,368)
(First) onset during 2020-2022	1.7 (42,068)	2.0 (28,783)	1.4 (13,285)
Present before 2020	8.1 (196,939)	8.8 (128,050)	7.1 (68,889)
Tuberculosis (ongoing episode)			
Absent throughout 2020-2022	96.8 (2,351,220)	96.2 (1,400,628)	97.5 (950,592)
Experienced an episode during 2020-2022	3.2 (78,707)	3.8 (54,757)	2.5 (23,950)

^a Complete vaccination: ≥ 28 days since a first Ad26.COV2.S dose or ≥ 14 days since a second dose following a first BNT162b2 dose (see methods).

^b Tuberculosis (at any time in past) includes both ongoing and previous episodes.

Table 2: COVID-19 vaccination, SARS-CoV-2 testing, and COVID-19 outcomes all as at end 2022, in the cohort of South African adults utilising public sector healthcare in the Western Cape province, studied during calendar years 2020 through 2022, also stratified by completion of a primary COVID-19 vaccination series by end 2022. Percent (count frequency) is reported.

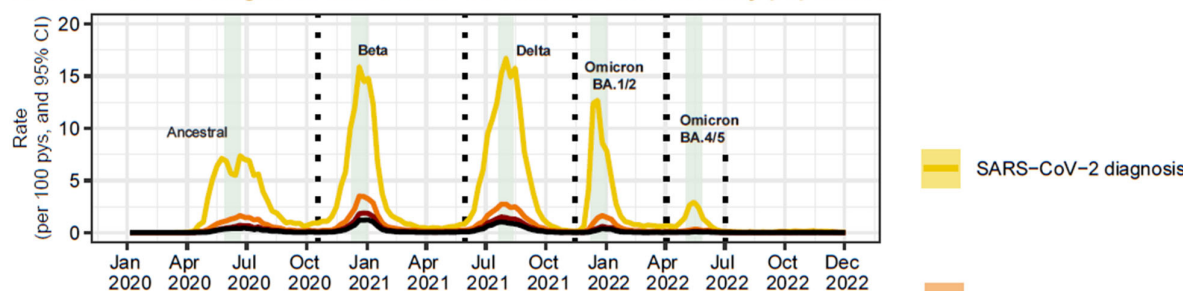
State or events experienced as at end 2022	Overall N = 2,429,927	Complete vaccination by end 2022 ^a	
		No N = 1,455,385	Yes N = 974,542
COVID-19 vaccination status¹ and boosters			
None	55.0 (1,336,826)	91.9 (1,336,826)	0.0 (0)
Incomplete BNT162b2	4.9 (118,559)	8.1 (118,559)	0.0 (0)
Complete Ad26.COV2.S (no booster)	9.7 (236,725)	0.0 (0)	24.3 (236,725)
Complete Ad26.COV2.S (and booster)	1.7 (41,196)	0.0 (0)	4.2 (41,196)
Complete BNT162b2 (no booster)	22.6 (548,914)	0.0 (0)	56.3 (548,914)
Complete BNT162b2 (and booster)	6.1 (147,707)	0.0 (0)	15.2 (147,707)
SARS-CoV-2 diagnosis			
Not experienced	92.1 (2,237,396)	93.3 (1,357,422)	90.3 (879,974)
Experienced	7.9 (192,531)	6.7 (97,963)	9.7 (94,568)
Number of negative SARS-CoV-2 tests			
0	81.8 (1,987,267)	84.3 (1,227,129)	78.0 (760,138)
1	13.1 (317,758)	11.4 (165,723)	15.6 (152,035)
2+	5.1 (124,902)	4.3 (62,533)	6.4 (62,369)
COVID-19 related hospitalization, or death			
Not experienced	98.4 (2,391,586)	98.2 (1,429,692)	98.7 (961,894)
Experienced	1.6 (38,341)	1.8 (25,693)	1.3 (12,648)
COVID-19 related hospitalization with severe disease, or death			
Not experienced	99.3 (2,412,279)	99.0 (1,441,138)	99.7 (971,141)
Experienced	0.7 (17,648)	1.0 (14,247)	0.3 (3,401)
COVID-19 related death and vital status^b			
Alive	95.4 (2,318,859)	93.3 (1,357,339)	98.7 (961,520)
Died: not COVID-19 related	4.1 (99,525)	6.0 (87,001)	1.3 (12,524)
Died: COVID-19 related	0.5 (11,543)	0.8 (11,045)	0.1 (498)

^a Complete vaccination: ≥ 28 days since a first Ad26.COV2.S dose or ≥ 14 days since a second dose following a first BNT162b2 dose; incomplete BNT162b2: ≥ 21 days since a first BNT162b2 dose but not yet completely vaccinated (see methods).

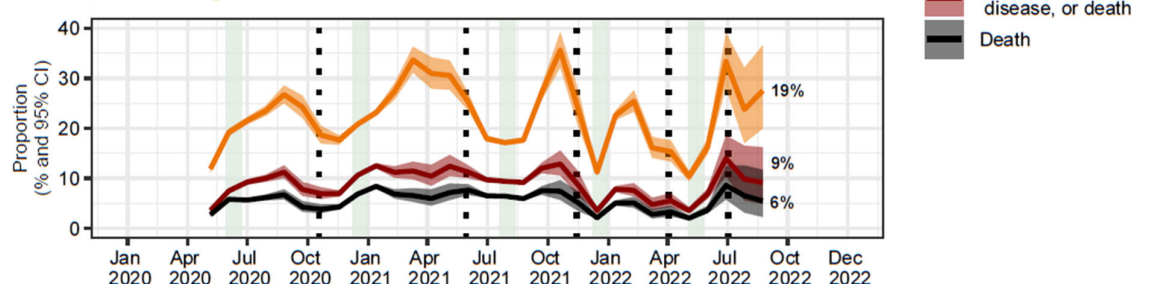
^b Based on the current (i.e., time-varying) complete primary vaccination status of the person (rather than at the end of the analysis period): Non-COVID death rate per 100 person years in unvaccinated and vaccinated persons was 1.4 and 1.0 respectively; COVID death rate in unvaccinated and vaccinated persons was 0.2 and 0.04 respectively.

Figure 1: COVID-19 outcomes, SARS-CoV-2 testing and positivity, and COVID-19 vaccination in the cohort of South African adults utilising public sector healthcare in the Western Cape province, over time, through the COVID-19 pandemic period. (A) Rates of SARS-CoV-2 diagnoses and COVID-19-associated hospitalisation and death outcomes, per week (B) Proportions of persons with SARS-CoV-2 diagnoses who experienced COVID-19 outcomes, per 4-week period, with overall proportions over the full plotted period indicated. (C) SARS-CoV-2 test positivity proportions, per week. (D) Proportions of the population in different vaccine states, at the end of each calendar month. Dashed vertical lines separate wave periods. Grey vertical bands indicate each wave's peak SARS-CoV-2 diagnoses weeks.

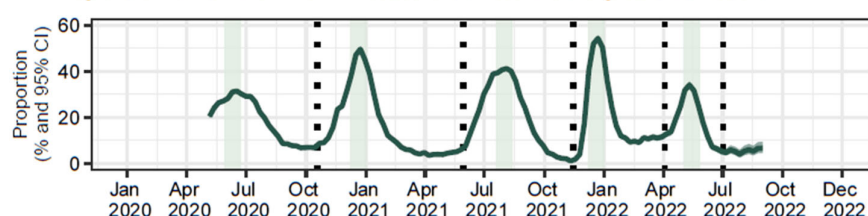
A: SARS-CoV-2 diagnosis and COVID-19 outcome rates in study population



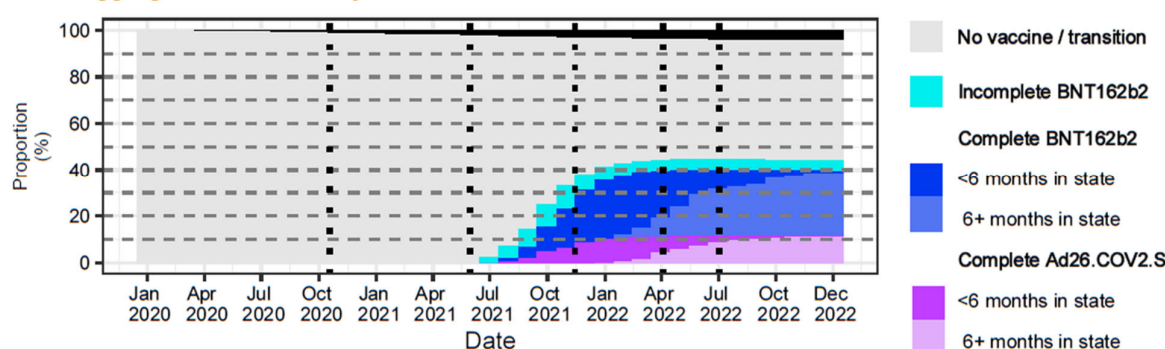
B: Proportion diagnosed with SARS-CoV-2 who had a COVID-19 outcome^a



C: Proportion of SARS-CoV-2 tests that returned a positive result^a



D: Disaggregation of cohort by vaccination^b and vital status

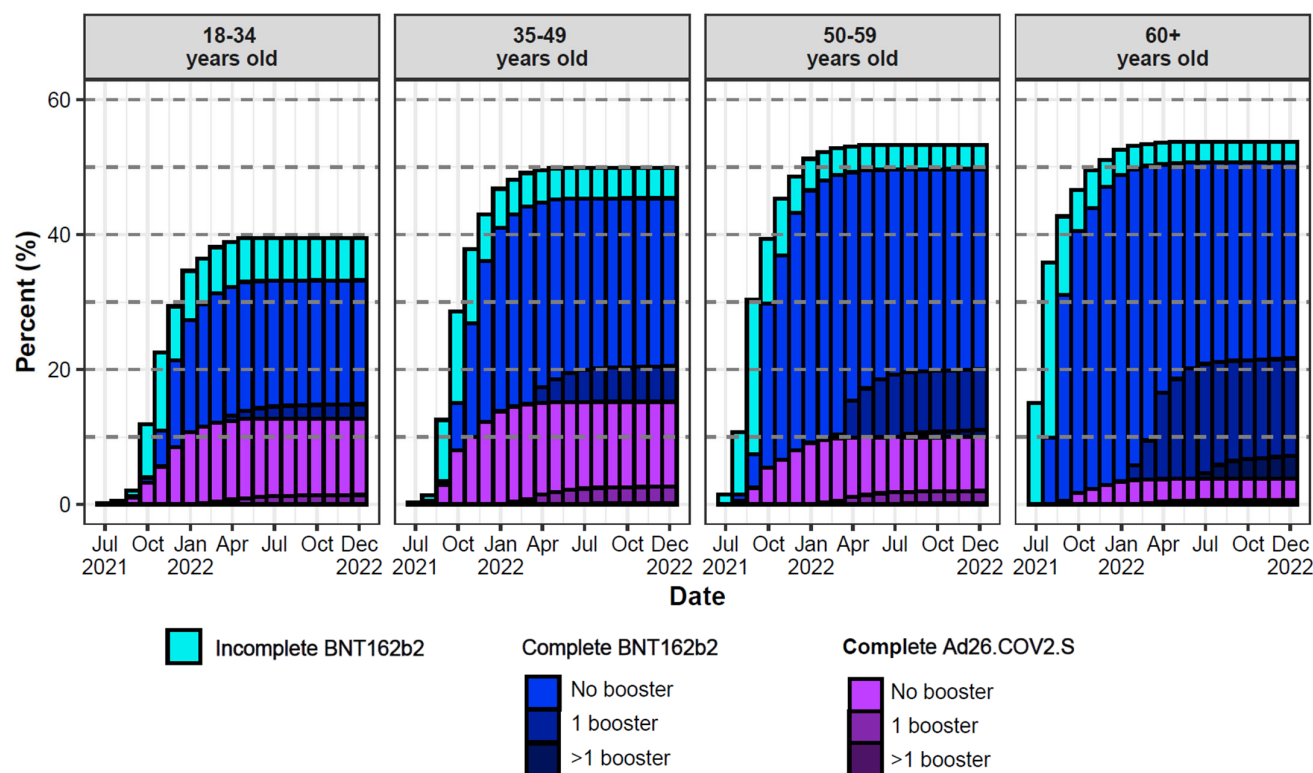


CI: confidence interval. pys: person-years.

^a Proportions are not shown for first and last months due to large uncertainties from few diagnoses/tests

^b See methods. No vaccine/transition: No dose received or <28 days after first Ad26.COVS.S dose or <21 days after first BNT162b2 dose; incomplete BNT162b2: ≥21 days since a first BNT162b2 dose but not yet completely vaccinated; complete BNT162b2: ≥14 days since a second dose following a first BNT162b2 dose; complete Ad26.COVS.S: ≥28 days since a first Ad26.COVS.S dose. Time in state is reset 7 days following a booster

Figure 2: Primary series vaccination and booster uptake in the cohort of South African adults utilising public sector healthcare in the Western Cape province: Proportions of the surviving population in the different vaccinated states^a, at the end of each calendar month (x-axis), by age group in years (based on age at start 2020) (figure columns).



^a Incomplete BNT162b2: ≥ 21 days since a first BNT162b2 dose but not yet completely vaccinated; complete BNT162b2: ≥ 14 days since a second dose following a first BNT162b2 dose; complete Ad26.COV2.S: ≥ 28 days since a first Ad26.COV2.S dose.

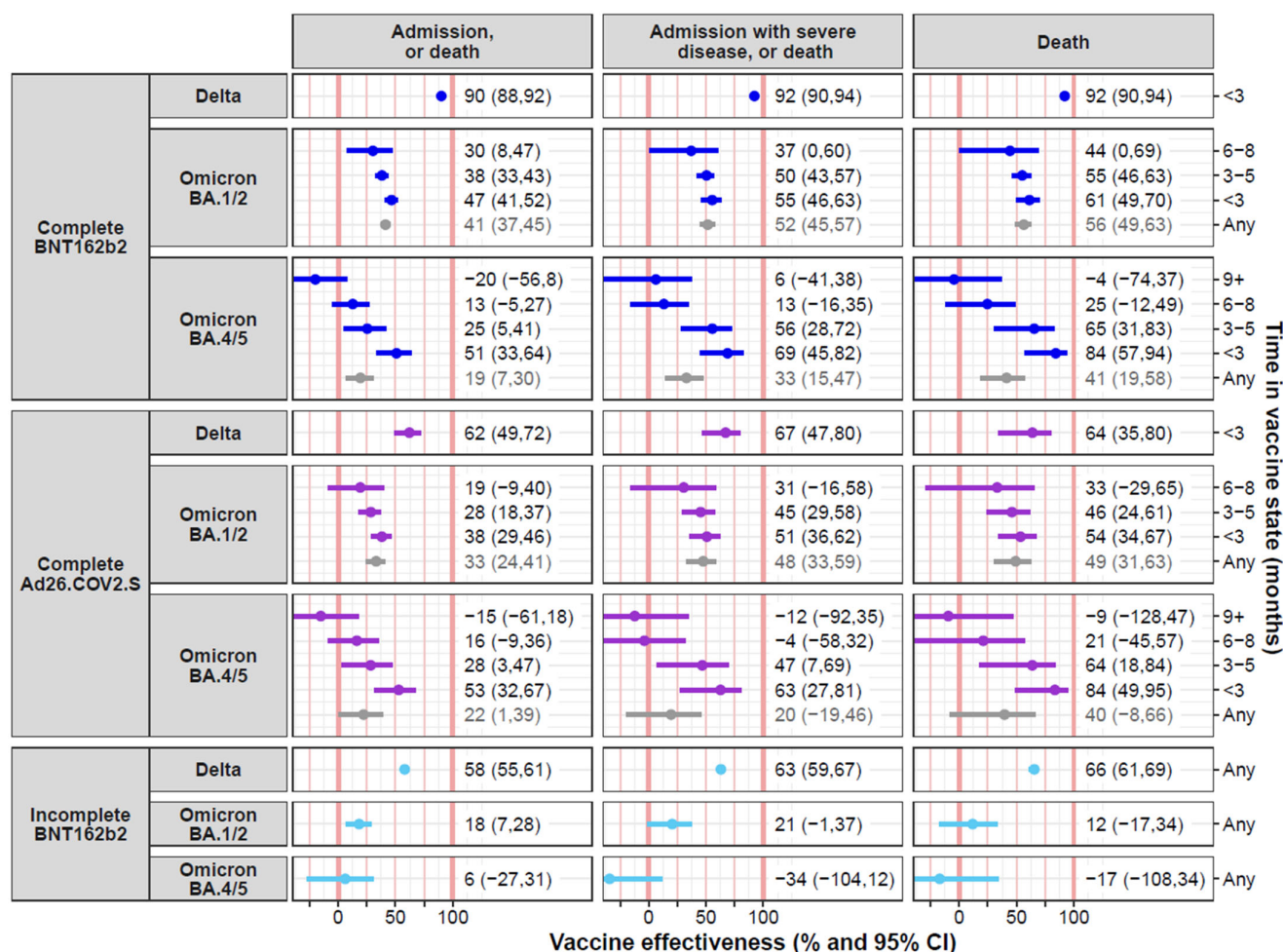
Vaccine effectiveness estimates

Before adjusting for time in vaccinated state, there was substantial variation in estimated VE by COVID-19 outcome and wave period (**Figure 3**): outcome rates ranged from 20 to 92% lower in completely vaccinated (versus unvaccinated). When accounting for time in vaccine state, VE was high among those who most recently completed or boosted vaccination (i.e., within three months), for all wave periods and outcomes – point estimates were in the range of 54-92% for death, 51-92% for admission with severe disease or death, and 38-90% for any admission or death. However, there was a distinct reduction of VE with longer durations after completing or boosting vaccination – on average, VE point estimates reduced by about 25% then 50% when moving from <3 months to 3-5 months and then to 6-8 month post-vaccination in turn, though uncertainties often became large at 6-8 months.

Considering the type of vaccine, within 3 months of completing or boosting vaccination in the Delta wave, at a point estimate level, the VE of BNT162b2 (90-92% across outcomes) was higher than for Ad26.COV2.S (62-67%), while the two vaccines' VE were often more similar over the Omicron periods for similar times in vaccine state. During the most recent Omicron BA.4/5 period and for the most severe outcome of death, within 3 months, BNT162b2 and Ad26.COV2.S were each 84% effective against death (95% CIs: 57-94 and 49-95, respectively).

We were unable to detect differences in VE by HIV status (p-values for LRTs by outcome and wave periods mostly $\gg 0.05$). **Appendix B3** reports VE estimates for subpopulations, which all had reduced rates of outcomes when recently vaccinated, though uncertainties can be large. **Appendix B4** presents estimated hazard ratios for all covariates in the multivariable cox models. **Appendix B5** demonstrates the steady decline in VE measured over 6-week rolling windows of time that could be explained by factors such as increasing times in vaccine state (not accounted for in this analysis), testing practices, and growing mismatch between vaccine and dominant infection (sub)lineage. **Appendix A5** presents a theoretical exploration of the magnitude of bias in estimating VE resulting from the under-ascertainment of prior infection.

Figure 3: Vaccine effectiveness estimates (x-axis), for different vaccinated states^a and wave periods (figure rows) and COVID-19 outcomes (figure columns), by time^b in the vaccinated state (y-axis). Vaccine effectiveness represents the reduction in outcome rates for vaccinated persons versus unvaccinated persons, adjusting for all covariates. Markers indicate point estimates, horizontal error bars represent 95% confidence intervals.



^a Complete vaccination: ≥ 28 days since a first Ad26.COV2.S dose or ≥ 14 days since a second dose following a first BNT162b2 dose; incomplete BNT162b2: ≥ 21 days since a first BNT162b2 dose but not yet completely vaccinated (see methods).

^b Estimates in grey (corresponding to 'Any' time in vaccine state) are obtained from a separate model which does not distinguish by time in the vaccine state, but still adjusts for all covariates, for comparison purposes.

Discussion

To our knowledge, this is the largest observational cohort study of COVID-19 VE in an African population with high levels of infection before vaccines became available and low overall vaccination uptake; and ongoing updates of this study's results were used in real-time to inform SA's vaccination programme. By end 2022, only 41% of adults had received primary vaccination and 8% a booster. VE against severe COVID-19 involving hospitalisation or death was high within 3 months of completing or boosting vaccination, including during periods when more recent Omicron (sub)lineages dominated: BNT162b2 and Ad26.COV2S were >80% effective against death during the Omicron BA.4/5 period, and VE point estimates varied within 38-92% across distinct wave periods and outcomes. However, we found distinct reductions of VE at larger times post completing or boosting vaccination during the Omicron periods.

Our assessment of VE durability against severe COVID-19 following recent primary or booster vaccination in a setting of high levels of SARS-CoV-2 infection before vaccination provides an important extension of results from others settings: a systematic review including five studies of hybrid protection conferred by both confirmed prior infection and vaccination against severe COVID-19 (hospitalisations or severe disease) showed durable protective VE >90% (compared to persons unvaccinated without prior infection) for up to 12 months following primary vaccination and 6 months following boosting, before and during the Omicron period.^{2,20-24} However, the review did not include any studies from Africa or settings with high levels of SARS-CoV-2 infection before Omicron emergence,^{5,25} follow-up after booster vaccination was limited and results were variable.^{21,23}

Our results from a cohort study are not directly comparable with these mostly test-negative case-control studies which examined the association of COVID-19 outcomes with confirmed hybrid protection (vaccination and prior infection) specifically in samples of only people with respiratory symptoms and testing for SARS-CoV-2 infection. Our study considered a general population, and, given the substantial under-ascertainment of SARS-CoV-2 infections in our setting, we could not robustly assess hybrid immunity. However, our results of high VE that reduced at longer durations post-vaccination were similar to three studies of severe COVID-19 during the Omicron period included in the review: In a Swedish study, VE from hybrid immunity was >80% after ≥ 3 vaccine doses but 54% (95% CI: 13,75) with only 2 doses.²⁴ In a Czech study, VE conferred by hybrid immunity declined at >2 months since last vaccine (primary series or booster).²¹ In a USA study, among people with prior infection and ≥ 5 months after primary vaccination, the VE of boosting was 56% (95% CI: 44,66).²⁶

Strengths of our study include using routinely collected longitudinal observational data to assess real-world VE with a cohort design in a large population of relevance to many LMICs. We had robust ascertainment of vaccination through linkage to EVDS; and of SARS-CoV-2 testing, admissions, and deaths, through linkage to NICD records and vital registration. We also adjusted for known health conditions, health service utilisation and testing behaviour.

Using routinely collected observational data also confers several limitations. First, there may be unmeasured confounding. For example, from a healthy vaccinee bias (inflating VE measures)²⁷ or greater health-seeking behaviour for COVID-19 disease among the vaccinated (deflating VE measures). Our adjustment for prior SARS-CoV-2 infections was also extremely limited – there was substantial under-ascertainment of infections in the WC throughout the pandemic, which likely increased with the

emergence of the Omicron lineage.⁶ Second, low booster uptake limited our ability to assess the effectiveness of boosters themselves or distinguish between homologous/heterologous boosting.¹⁴ Third, there may be misclassification of outcomes. Identifying the outcome required a positive SARS-CoV-2 test in those admitted or deceased, which would be impacted by testing practices and the use of antigen (versus PCR) tests which varied over time. We have previously shown the decrease in the specificity of identifying COVID-19 related hospitalisations and deaths with the emergence of Omicron BA.1/2 and widespread testing of all admitted patients.²⁸²⁹ This may contribute to a deflation in VE estimates in this study during the Omicron BA.1/2 wave, compared to in the BA.4/5 wave when only those with clinically suspected COVID-19 were tested. Also, data on recorded steroid prescription to identify ‘admissions with severe disease’ were only available for public sector admissions. Lastly, we were only able to assess changes in VE with time post-vaccination during the later Omicron periods.

Conclusions

Even in our population with high levels of immunity from prior infection, recently completing or boosting COVID-19 vaccination (<6 months previously) provided protection against severe COVID-19, but this protection reduced at longer durations since last vaccine dose. Continued opportunities for COVID-19 primary vaccination and boosting of vulnerable populations should be provided irrespective of levels of prior SARS-CoV-2 infection.

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AB, RK and MD conceived the study. AH prepared the data extracts. RK designed and implemented the analysis, with inputs from MD, AB and LH. RK drafted and revised the manuscript, with contributions by MD. All authors reviewed the manuscript, provided inputs and approved the manuscript.

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Data is not publicly available.

Conflicts of interest

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References

1. Wise J. COVID-19: WHO declares end of global health emergency. *BMJ* 2023;381:p1041.
2. Bobrovitz N, Ware H, Ma X, et al. Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression. *Lancet Infect Dis* 2023;23:556-67.
3. Feikin DR, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *Lancet* 2022;399:924-44.
4. Menegale F, Manica M, Zardini A, et al. Evaluation of waning of SARS-CoV-2 vaccine-induced immunity: A systematic review and meta-analysis. *JAMA Netw Open* 2023;6:e2310650.
5. Madhi SA, Kwatra G, Myers JE, et al. Population immunity and COVID-19 severity with Omicron variant in South Africa. *The New England Journal of Medicine* 2022;386:1314-26.
6. Hussey H, Vreede H, Davies M-A, et al. Epidemiology and outcomes of SARS-CoV-2 infection associated with anti-nucleocapsid seropositivity in Cape Town, South Africa. *medRxiv* 2022:2022.12.01.22282927.
7. Mutombo PN, Fallah MP, Munodawafa D, et al. COVID-19 vaccine hesitancy in Africa: a call to action. *The Lancet Global health* 2022;10:e320-e1.
8. Brazier E, Ajeh R, Maruri F, et al. Service delivery challenges in HIV care during the first year of the COVID-19 pandemic: results from a site assessment survey across the global IeDEA consortium. *Journal of the International AIDS Society* 2022;25:e26036.
9. Harris TG, Jaszi E, Lamb MR, et al. Effects of the Coronavirus Disease 2019 Pandemic on Human Immunodeficiency Virus Services: Findings from 11 Sub-Saharan African Countries. *Clinical Infectious Diseases* 2022;75:e1046-e53.
10. Wagner Z, Mukasa B, Nakakande J, Stecher C, Saya U, Linnemayr S. Impact of the COVID-19 pandemic on use of HIV care, Antiretroviral therapy adherence, and viral suppression: An observational cohort study from Uganda. *JAIDS* 2021;88:448-56.
11. Dear N, Duff E, Esber A, et al. Transient reductions in Human Immunodeficiency Virus (HIV) clinic attendance and food security during the Coronavirus Disease 2019 (COVID-19) pandemic for people living with HIV in 4 African countries. *Clinical Infectious Diseases* 2021;73:1901-5.
12. Collie S, Nayager J, Bamford L, Bekker LG, Zylstra M, Gray G. Effectiveness and durability of the BNT162b2 vaccine against Omicron sublineages in South Africa. *The New England Journal of Medicine* 2022;387:1332-3.
13. Boulle A, Heekes A, Tiffin N, et al. Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. *International Journal of Population Data Science* 2019;4.
14. Department of Health, Republic of South Africa. COVID-19 Online Resource and New Portal: Latest Vaccine Statistics. [Accessed 31 December 2023, at <https://sacoronavirus.co.za/latest-vaccine-statistics>].

15. National Institute for Communicable Diseases. COVID-19 Surveillance Reports. [Accessed 13 October 2023 at <https://www.nicd.ac.za/diseases-a-z-index/disease-index-covid-19/surveillance-reports>].
16. Jassat W, Karim S, Mudara C, et al. Clinical severity of COVID-19 patients admitted to hospitals in Gauteng, South Africa during the Omicron-dominant fourth wave. *Lancet preprints* 2021.
17. Jassat W, Mudara C, Ozougwu L, et al. Difference in mortality among individuals admitted to hospital with COVID-19 during the first and second waves in South Africa: a cohort study. *The Lancet Global health* 2021;9:e1216-e25.
18. Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases SA. Risk Factors for Coronavirus Disease 2019 (COVID-19) Death in a Population Cohort Study from the Western Cape Province, South Africa. *Clinical Infectious Diseases* 2020;73:e2005-e15.
19. Davies MA, Kassanjee R, Rousseau P, et al. Outcomes of laboratory-confirmed SARS-CoV-2 infection in the Omicron-driven fourth wave compared with previous waves in the Western Cape Province, South Africa. *Trop Med Int Health* 2022;27:564-73.
20. Carazo S, Skowronski DM, Brisson M, et al. Protection against omicron (B.1.1.529) BA.2 reinfection conferred by primary omicron BA.1 or pre-omicron SARS-CoV-2 infection among health-care workers with and without mRNA vaccination: a test-negative case-control study. *Lancet Infect Dis* 2023;23:45-55.
21. Šmíd M, Berec L, Příbylová L, et al. Protection by vaccines and previous infection against the Omicron variant of Severe Acute Respiratory Syndrome Coronavirus 2. *J Infect Dis* 2022;226:1385-90.
22. Altarawneh HN, Chemaitelly H, Ayoub HH, et al. Effects of previous infection and vaccination on symptomatic Omicron infections. *The New England Journal of Medicine* 2022;387:21-34.
23. Cerqueira-Silva T, de Araujo Oliveira V, Paixão ES, et al. Vaccination plus previous infection: protection during the Omicron wave in Brazil. *Lancet Infect Dis* 2022;22:945-6.
24. Björk J, Bonander C, Moghaddassi M, et al. COVID-19 vaccine effectiveness against severe disease from SARS-CoV-2 Omicron BA.1 and BA.2 subvariants - surveillance results from southern Sweden, December 2021 to March 2022. *Euro Surveill* 2022;27.
25. Madhi SA, Kwatra G, Myers JE, et al. South African population immunity and severe COVID-19 with Omicron variant. *medRxiv* 2021:2021.12.20.21268096.
26. Plumb ID, Feldstein LR, Barkley E, et al. Effectiveness of COVID-19 mRNA vaccination in preventing COVID-19-associated hospitalization among adults with previous SARS-CoV-2 infection - United States, June 2021-February 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:549-55.
27. Nichol KL. Challenges in evaluating influenza vaccine effectiveness and the mortality benefits controversy. *Vaccine* 2009;27:6305-11.
28. Paleker M, Davies MA, Raubenheimer P, Naude J, Boule A, Hussey H. Change in profile of COVID-19 deaths in Western Cape Province, South Africa, during the fourth wave. *South African Medical Journal* 2022;112:185-6.

29. UK Health Security Agency. Changes to the way we report on COVID-19 deaths [Accessed 8 January 2024, at <https://ukhsa.blog.gov.uk/2023/01/27/changes-to-the-way-we-report-on-covid-19-deaths>].