Supplementary Appendix

Supplement to: Collie S, Nayager J, Bamford L, et al. Effectiveness and durability of the BNT162b2 vaccine against omicron sublineages in South Africa. N Engl J Med. DOI: 10.1056/NEJMc2210093

This appendix has been provided by the authors to give readers additional information about the work.

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Methods

The population under study were patients that had been hospitalized for medical treatment in South Africa from the 15th November 2021 to the 24th June 2022. We applied a test-negative design to estimate vaccine effectiveness against COVID19 admission for Discovery clients vaccinated with 2 or 3 doses of a homologous series of BNT162b2 (Pfizer), for the time periods 15 Nov 2021 to 28 Feb 2022 (proxy BA1/BA2) or 15 April – 24 June 2022 (proxy BA4/BA5) period. Additionally, sub-population vaccine effectiveness estimates were determined for the entire period, 15 November – 24 June 2022 (a period of omicron variant circulation) in South Africa (Supplementary table 8).

Data

COVID19 PCR test results related to in-hospital admission data from Discovery Health's in-hospital pre-authorization system was extracted where the date of admission was in the proxy BA1/BA2 (15 Nov 2021 to 28 Feb 2022) or BA4/BA5 (15 April – 24 June 2022) period. COVID19 PCR test results associated with admissions unlikely to be related to COVID19 treatment were excluded e.g. cataract removals, musculoskeletal surgery, etc. This was based on a clinical exclusion list using Discovery Health's Diagnosis Related Groupings determined from WHO ICD-10 coding and CCSA procedure coding. More details can be provided on request.

Positive cases in the test-negative design were treated in-hospital for COVID19 related treatment, whereas negative cases were treated in-hospital due to other underlying reasons.

Vaccination status of clients was determined from medical claims-based data of patients vaccinated at both public and private vaccination sites.

The following data exclusions rules were applied[1]:

- Negative tests within 21 days of a positive test
- Negative tests within 7 days of another negative test result
- Positive and negative results within 6 weeks of a previous positive test result
- No more than 3 test results per patient were included in the study. Patients with more than three test results, contributed a random selection of three test results

Furthermore, indeterminate test results, test results for individuals younger than age 18, or test results for individuals who joined the medical scheme over the study period (i.e. individuals with unknown prior vaccination history), or test results for individuals vaccinated with a single dose of Pfizer or a dose of J&J are excluded. During the analysis period, booster doses i.e. a third vaccine dose became available to the South African public on 29 December 2021.

Statistical analysis

The data were adjusted for the following confounders: age (18-29, then 10-year age bands and then age 80+), sex, number of documented CDC risk factors (0,1,2,3+), surveillance week, period of prior documented infection (D614G variant period:2020/03/01-2020/10/31, Beta variant period:2020/11/01-2021/05/16, Delta variant period: 2021/05/17-2021/10/31, and Omicron variant period: 2021/11/01-2022/03/06), and geographic region (province) [Supplementary table 3].

Vaccine effectiveness estimates were obtained from the following formula: 1- odds ratio of COVID19 admission amongst the admitted vaccinated population, where the odds ratio was calculated using

logistic regression, adjusting for confounders. COVID19 admission was a dependent variable, while vaccination status was included as an independent variable. Vaccination coefficient estimates were exponentiated from the logistic regression model to obtain the adjusted odds ratio using the following calculation:

$$Adjusted\ odds\ ratio = e^{\beta}$$

$$where\ \beta\ denotes\ the\ beta\ coefficient\ estimate\ of\ vaccination\ status\ from\ the\ logistic\ regression\ model$$

95% confidence intervals (CIs) of the adjusted odds ratio were derived from the associated standard error estimates from the logistic regression for vaccination status using the following formula:

$$95\%CI\ (Lower, Upper)\text{: } (e^{\beta - 1.96 \times \sigma_x}, e^{\beta + 1.96 \times \sigma_x})$$

$$where\ \ \sigma_x = the\ standard\ error\ of\ the\ vaccination\ status\ estimate\ from\ the\ logistic\ regression\ model$$

By way of example, Table S1 provides the number of positive and negative test results amongst the unvaccinated and a subset of the vaccinated admitted population. The vaccinated population includes those vaccinated with their second dose 3-4 months ago.

The odds of COVID19 admission amongst those vaccinated in this example is: (758/5106)/(1931/5896)=45.3%, therefore vaccine effectiveness (without adjustment for confounders) is 54.7% (1-45.3%).

Test negative case control studies have been applied to assess vaccinations for a range of diseases [2]. The design specifies cases as individuals who tested positive with COVID19 and controls with a negative test. The design of the study looks to overcome and control for healthcare seeking behavior through selection of individuals who have both tested. The core assumption of the test negative design is that the intervention (vaccine) has no effect on other diseases with similar symptoms. We tested this assumption by assessing the distribution of vaccination status amongst our test negative controls with the distribution of vaccination status from the full underlying population [3] (Supplementary table 4). Another key assumption is that positive results emanate from highly specific testing. Positive tests were obtained from COVID19 PCR test results, which are highly specific. Furthermore, the design requires that test results are assessed on a symptomatic population, to avoid bias arising due to a different testing propensity amongst those vaccinated and controls.

Vaccination status was analyzed in the following categories (not vaccinated; 0-13, 14-27, 28-87 (one to two months), 88-147 (three to four months), 148-207 (five to six months), 208-267 (seven to eight months), and 268 days(nine months) onwards since last dose of vaccination.

A sensitivity analysis was performed using only COVID19 PCR results amongst patients admitted in Gauteng, South Africa's most populous province.

Calculations were performed using R version 4.1.2

Figure S1: Genomic sequences by variant type in South Africa by calendar date (Source: Network for Genomic Surveillance in South Africa- SARS COV2 Genomic Surveillance update (24 June 2022))

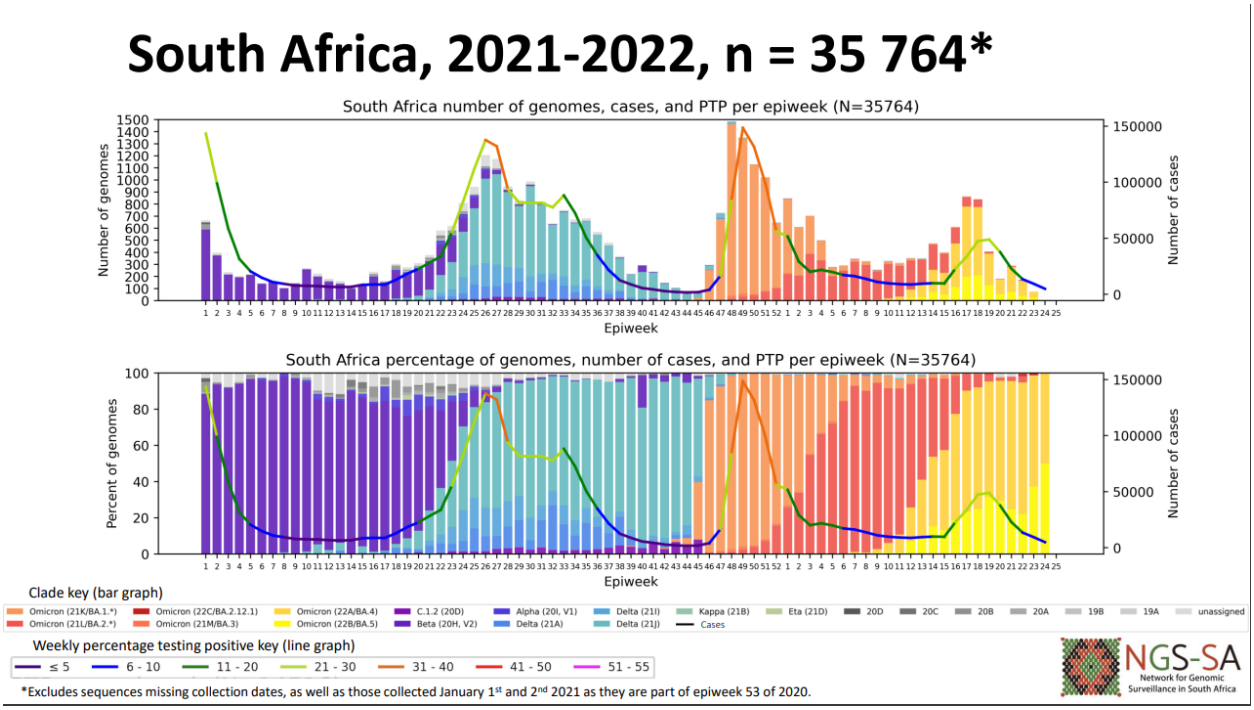


Figure S2: Frequency distribution (%) of breakthrough infections (BTIs) vs percentage frequency distribution of COVID19 admissions Pfizer vaccinated Discovery clients (14 days+ since dose 2 vaccination and 14+ days since dose 3 vaccination) between 15 November 2021-and 24 June 2022 (proxy Omicron period) by age band.

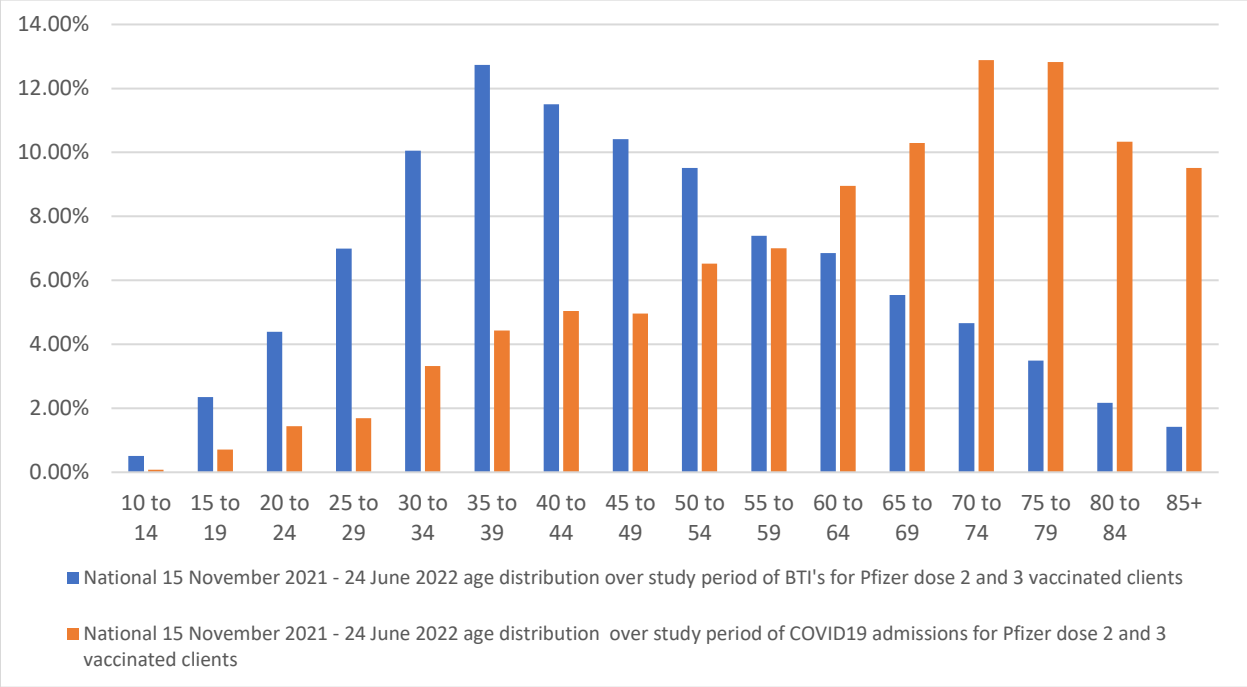
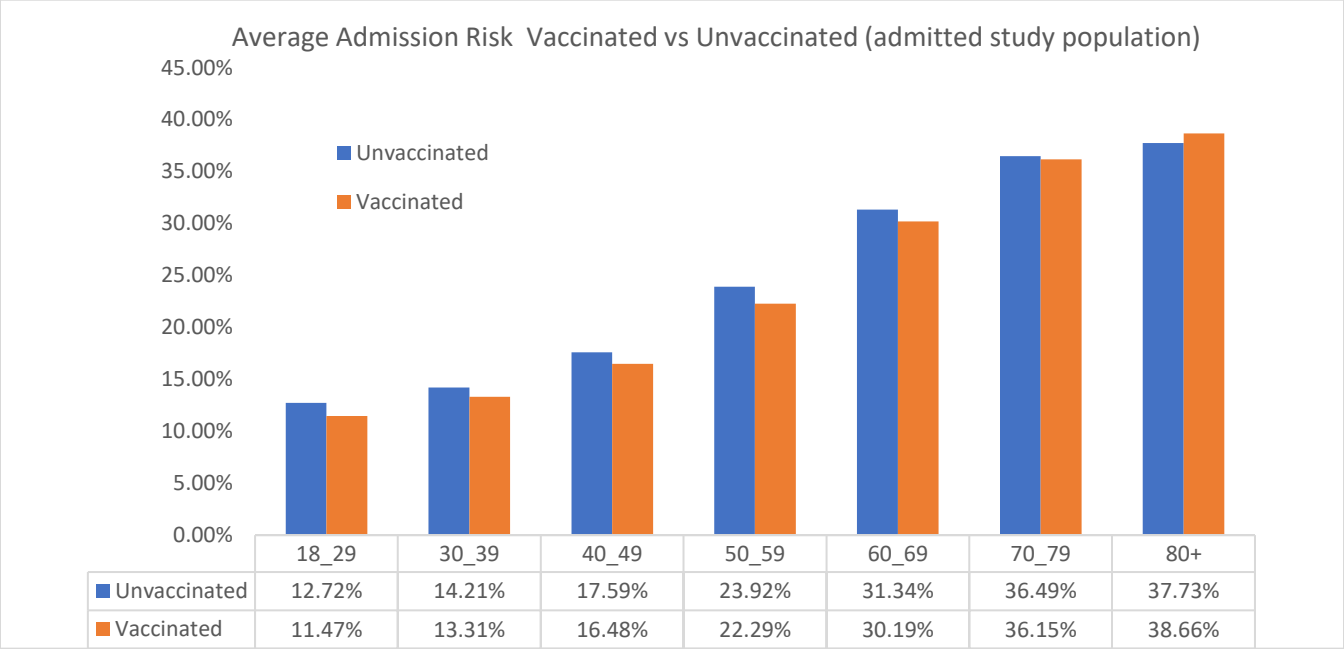


Figure S3: Distribution of the average admission risk* by age group split by vaccinated and unvaccinated within the study population.

This is measured at the start of the Omicron period. Unvaccinated patients have admission risk similar to those vaccinated, across age groups.



	18_29	30_39	40_49	50_59	60_69	70_79	80+
Unvaccinated	12.72%	14.21%	17.59%	23.92%	31.34%	36.49%	37.73%
Vaccinated	11.47%	13.31%	16.48%	22.29%	30.19%	36.15%	38.66%

*To calculate admission risk, we used a separate predictive model used by the managed care organisation, which is determined using the following factors:

- *Chronic conditions for which a member was registered*
- *Demographic factors such as age, sex and type of medical scheme plan purchased*
- *The type of physician practices that member attended in the prior 12 months (i.e. practice speciality type)*
- *Medicines for which a member had claimed in the prior 12 months*
- *Procedures and consultations for which a member had claimed in the prior 12 months*
- *WHO-ICD10 information from claims submitted in the prior 12 months*

Table S1: Test results by vaccination status in proxy BA1/BA2 period

	COVID19 PCR test result		
	Positive	Negative	Total
Vaccinated (3-4 months since dose 2)	758	5106	5864
Not vaccinated	1931	5896	7827
Total	2689	11002	13691

Table S2: A consort table to show individuals included in the study 15 November 2021-24 June 2022.

	Number of tests (%)
Total tests from 15 November 2021 - 24 June 2022	73,963 (100%)
Negative Test within 21 days of positive	1,631 (2.2%)
Negative test in the prior 7 days of another negative test	4,562 (6.2%)
Prior positive test within last 90 days	1,211 (1.6%)
Result missing	204 (0.3%)
Age less than 12	16,098 (21.8%)
New Scheme Joiners Excluded	1,237 (1.7%)
Other vaccine regiments excluded from study	8,914 (12.1%)
Not chosen as 3 random tests	1,739 (2.4%)
Included in study	38,367 (51.9%)

Table S3: Baseline characteristics of the study population.

	15 November-24 June 2022 ("proxy omicron period")		Sensitivity: Gauteng	
(n,%)	Tests	Positive COVID19 tests	Tests	Positive COVID19 tests
Age (in years)				
18-29	2,299 (5.99%)	483 (1.26%)	1,067 (2.78%)	218 (0.57%)
30-39	4,095 (10.67%)	801 (2.09%)	1,810 (4.72%)	331 (0.86%)
40-49	4,948 (12.9%)	813 (2.12%)	2,146 (5.59%)	327 (0.85%)
50-59	5,821 (15.17%)	851 (2.22%)	2,333 (6.08%)	324 (0.84%)
60-69	7,617 (19.85%)	1,045 (2.72%)	2,923 (7.62%)	357 (0.93%)
70-79	8,198 (21.37%)	1,368 (3.57%)	3,081 (8.03%)	483 (1.26%)
80+	5,389 (14.05%)	1,074 (2.8%)	1,956 (5.1%)	367 (0.96%)
Sex				
Male	19,603 (51.09%)	3,439 (8.96%)	8,093 (21.09%)	1,319 (3.44%)
Female	18,764 (48.91%)	2,996 (7.81%)	7,223 (18.83%)	1,088 (2.84%)
Number of CDC risk factors**				
0	10,868 (28.33%)	2,011 (5.24%)	4,664 (12.16%)	817 (2.13%)
1	8,898 (23.19%)	1,440 (3.75%)	3,642 (9.49%)	542 (1.41%)
2	7,951 (20.72%)	1,265 (3.3%)	3,132 (8.16%)	460 (1.2%)
3+	10,650 (27.76%)	1,719 (4.48%)	3,878 (10.11%)	588 (1.53%)
Calendar week				
Year 2021 Week 46	1,104 (2.88%)	16 (0.04%)	442 (1.15%)	6 (0.02%)
Year 2021 Week 47	1,604 (4.18%)	47 (0.12%)	591 (1.54%)	26 (0.07%)
Year 2021 Week 48	1,729 (4.51%)	210 (0.55%)	702 (1.83%)	138 (0.36%)
Year 2021 Week 49	1,851 (4.82%)	440 (1.15%)	793 (2.07%)	229 (0.6%)
Year 2021 Week 50	1,518 (3.96%)	462 (1.2%)	548 (1.43%)	165 (0.43%)
Year 2021 Week 51	1,374 (3.58%)	495 (1.29%)	508 (1.32%)	151 (0.39%)
Year 2021 Week 52	1,235 (3.22%)	486 (1.27%)	439 (1.14%)	133 (0.35%)
Year 2022 Week 1	153 (0.4%)	70 (0.18%)	61 (0.16%)	20 (0.05%)
Year 2022 Week 2	1,470 (3.83%)	402 (1.05%)	519 (1.35%)	110 (0.29%)
Year 2022 Week 3	1,647 (4.29%)	275 (0.72%)	662 (1.73%)	78 (0.2%)
Year 2022 Week 4	1,678 (4.37%)	203 (0.53%)	653 (1.7%)	61 (0.16%)
Year 2022 Week 5	1,766 (4.6%)	181 (0.47%)	676 (1.76%)	51 (0.13%)

	15 November-24 June 2022 ("proxy omicron period")		Sensitivity: Gauteng	
(n,%)	Tests	Positive COVID19 tests	Tests	Positive COVID19 tests
Year 2022 Week 6	1,748 (4.56%)	161 (0.42%)	667 (1.74%)	53 (0.14%)
Year 2022 Week 7	1,623 (4.23%)	156 (0.41%)	650 (1.69%)	50 (0.13%)
Year 2022 Week 8	1,339 (3.49%)	136 (0.35%)	524 (1.37%)	40 (0.1%)
Year 2022 Week 9	1,154 (3.01%)	110 (0.29%)	480 (1.25%)	37 (0.1%)
Year 2022 Week 10	1,060 (2.76%)	101 (0.26%)	427 (1.11%)	46 (0.12%)
Year 2022 Week 11	971 (2.53%)	83 (0.22%)	377 (0.98%)	21 (0.05%)
Year 2022 Week 12	885 (2.31%)	69 (0.18%)	354 (0.92%)	26 (0.07%)
Year 2022 Week 13	825 (2.15%)	71 (0.19%)	338 (0.88%)	23 (0.06%)
Year 2022 Week 14	840 (2.19%)	70 (0.18%)	327 (0.85%)	23 (0.06%)
Year 2022 Week 15	810 (2.11%)	82 (0.21%)	341 (0.89%)	34 (0.09%)
Year 2022 Week 16	660 (1.72%)	87 (0.23%)	277 (0.72%)	38 (0.1%)
Year 2022 Week 17	784 (2.04%)	152 (0.4%)	321 (0.84%)	67 (0.17%)
Year 2022 Week 18	909 (2.37%)	247 (0.64%)	399 (1.04%)	114 (0.3%)
Year 2022 Week 19	1,029 (2.68%)	283 (0.74%)	449 (1.17%)	126 (0.33%)
Year 2022 Week 20	1,109 (2.89%)	314 (0.82%)	472 (1.23%)	138 (0.36%)
Year 2022 Week 21	1,092 (2.85%)	299 (0.78%)	474 (1.24%)	126 (0.33%)
Year 2022 Week 22	1,001 (2.61%)	218 (0.57%)	429 (1.12%)	90 (0.23%)
Year 2022 Week 23	900 (2.35%)	171 (0.45%)	368 (0.96%)	62 (0.16%)
Year 2022 Week 24	761 (1.98%)	107 (0.28%)	327 (0.85%)	43 (0.11%)
Year 2022 Week 25	834 (2.17%)	89 (0.23%)	338 (0.88%)	40 (0.1%)
Period of last documented prior infection				
None	31,434 (81.93%)	5,778 (15.06%)	12,293 (32.04%)	2,151 (5.61%)
Ancestral (2020/03/01-2020/10/31)	1,201 (3.13%)	105 (0.27%)	512 (1.33%)	47 (0.12%)
Beta (2020/11/01-2021/05/16)	1,681 (4.38%)	148 (0.39%)	552 (1.44%)	45 (0.12%)
Delta (2021/05/17-2021/10/31)	3,222 (8.4%)	279 (0.73%)	1,602 (4.18%)	109 (0.28%)
Omicron (2021/11/01-2022/04/14)	829 (2.16%)	125 (0.33%)	357 (0.93%)	55 (0.14%)
Province				
Eastern Cape	1,330 (3.47%)	243 (0.63%)	0 (0%)	0 (0%)

	15 November-24 June 2022 ("proxy omicron period")		Sensitivity: Gauteng	
(n,%)	Tests	Positive COVID19 tests	Tests	Positive COVID19 tests
Free State	1,607 (4.19%)	280 (0.73%)	0 (0%)	0 (0%)
Gauteng	15,316 (39.92%)	2,407 (6.27%)	15,316 (39.92%)	2,407 (6.27%)
KwaZulu Natal	7,729 (20.14%)	1,383 (3.6%)	0 (0%)	0 (0%)
Limpopo	568 (1.48%)	113 (0.29%)	0 (0%)	0 (0%)
Mpumalanga	1,310 (3.41%)	262 (0.68%)	0 (0%)	0 (0%)
North West	1,575 (4.11%)	282 (0.74%)	0 (0%)	0 (0%)
Northern Cape	466 (1.21%)	85 (0.22%)	0 (0%)	0 (0%)
Western Cape	7,224 (18.83%)	1,174 (3.06%)	0 (0%)	0 (0%)
Not allocated	1,242 (3.24%)	206 (0.54%)	0 (0%)	0 (0%)

Table S4: Characteristics of vaccinated and unvaccinated COVID-19 cases during Omicron

	Dose 2				Dose 3				Total (Dose 2& 3)			
	Proxy BA1/BA2 omicron period		**Proxy BA4/BA5 omicron period**		**Proxy BA1/BA2 omicron period**		**Proxy BA4/BA5 omicron period**		**Proxy BA1/BA2 omicron period**		**Proxy BA4/BA5 omicron period**	
	Tests	**Positive tests**	**Tests**	**Positive tests**	**Tests**	**Positive tests**	**Tests**	**Positive tests**	**Tests**	**Positive tests**	**Tests**	**Positive tests**
Not Vaccinated ("comparator")									7827 (30.4%)	1931 (7.5%)	3019 (11.7%)	768 (3%)
Pfizer - 0 to 13 days since last dose	166 (0.6%)	12 (0%)	5 (0%)	1 (0%)	360 (1.4%)	30 (0.1%)	36 (0.1%)	9 (0%)	526 (2%)	42 (0.2%)	41 (0.2%)	10 (0%)
Pfizer - 14 to 27 days since last dose	202 (0.8%)	11 (0%)	10 (0%)	0 (0%)	355 (1.4%)	14 (0.1%)	59 (0.2%)	9 (0%)	557 (2.2%)	25 (0.1%)	69 (0.3%)	9 (0%)
Pfizer - 1 to 2 months since last dose	2123 (8.2%)	237 (0.9%)	58 (0.2%)	6 (0%)	550 (2.1%)	46 (0.2%)	661 (2.6%)	76 (0.3%)	2673 (10.4%)	283 (1.1%)	719 (2.8%)	82 (0.3%)
Pfizer - 3 to 4 months since last dose	5864 (22.8%)	758 (2.9%)	174 (0.7%)	28 (0.1%)	85 (0.3%)	13 (0.1%)	1028 (4%)	191 (0.7%)	5949 (23.1%)	771 (3%)	1202 (4.7%)	219 (0.9%)
Pfizer - 5 to 6 months since last dose	5274 (20.5%)	771 (3%)	541 (2.1%)	112 (0.4%)	15 (0.1%)	1 (0%)	118 (0.5%)	16 (0.1%)	5289 (20.5%)	772 (3%)	659 (2.6%)	128 (0.5%)
Pfizer -7 to 8 months since last dose	639 (2.5%)	57 (0.2%)	1596 (6.2%)	343 (1.3%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	639 (2.5%)	57 (0.2%)	1597 (6.2%)	343 (1.3%)
Pfizer - post 9 months since last dose	0 (0%)	0 (0%)	2067 (8%)	469 (1.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2067 (8%)	469 (1.8%)

Table S5: Vaccination status amongst the test negative controls vs vaccine distribution in the whole underlying population November 2021 - June 2022.

	Negative control distribution	Positive and Negative distribution	All Discovery Health administered scheme adult population (scheme exposure)
Not Vaccinated	30.45%	32.88%	39.38%
Pfizer - 0 to 13 days post dose 2	0.51%	0.46%	1.53%
Pfizer - 14 to 27 days post dose 2	0.67%	0.59%	1.90%
Pfizer – 1 to 2 months post dose 2	6.37%	5.94%	9.73%
Pfizer -3 to 4 months post dose 2	17.32%	16.53%	11.35%
Pfizer -5 to 6 months post dose 2	18.32%	17.82%	10.50%
Pfizer -7 to 8 months post dose 2	9.45%	9.26%	8.00%
Pfizer - 9 months post dose 2	5.24%	5.62%	2.83%
Pfizer - 0 to 13 days post dose 3	1.41%	1.30%	1.67%
Pfizer - 14 to 27 days post dose 3	1.60%	1.42%	1.70%
Pfizer -1 to 2 months post dose 3	5.30%	4.81%	6.76%
Pfizer -3 to 4 months post dose 3	2.98%	3.02%	3.91%
Pfizer -5 to 6 months post dose 3	0.37%	0.35%	0.71%
Pfizer -7 to 8 months post dose 3	0.00%	0.00%	0.04%
Pfizer -9 months post dose 3	0.00%	0.00%	0.00%

Table S6: Table to show time since vaccination and number of tests conducted during each period.

	15 November 2021-24 June 2022				15 November 2021-24 June 2022- sensitivity (Gauteng admitted population)			
	Time since vaccination (in days)				Time since vaccination (in days)			
	Quartile 1	Median	Quartile 3	Number of Tests	Quartile 1	Median	Quartile 3	Number of Tests
Pfizer - 0 to 13 days post dose 2	4	7	11	175	4	7	10.5	83
Pfizer - 14 to 27 days post dose 2	17	21	25	226	17	20	25	109
Pfizer – 1 to 2 months post dose 2	51	66	78	2280	50	65	77	949
Pfizer -3 to 4 months post dose 2	108	124	136	6,341	107	123	136	2412
Pfizer -5 to 6 months post dose 2	161	175	189	6,837	161	175	190	2579
Pfizer -7 to 8 months post dose 2	219	233	249	3,552	219	235	249	1438
Pfizer - 9 months post dose 2	281	295	312	2156	281	295	312	831
Pfizer - 0 to 13 days post dose 3	4	7	10	498	5	7	11	205
Pfizer - 14 to 27 days post dose 3	17	20	24	544	17	20	24	213
Pfizer -1 to 2 months post dose 3	41	54	70	1,847	42	55	70	763
Pfizer -3 to 4 months post dose 3	98	111	126	1,159	98	110	124	443
Pfizer -5 to 6 months post dose 3	151	158	166	135	152	158	163	57
Pfizer -7 to 8 months post dose 3	220	220	220	1	220	220	220	1
Pfizer -9 months post dose 3								

Table S7: Vaccine effectiveness estimates from sensitivity analysis – Gauteng population

Vaccine Effectiveness*, (95% CI)	15 Nov 2021 to 28 Feb 2022 ("proxy BA1/BA2 omicron period")	15 April 2022-24 June 2022 ("proxy BA4/BA5 omicron period")
Pfizer - 0 to 13 days post dose 2		
Pfizer - 14 to 27 days post dose 2		
Pfizer – 1 to 2 months post dose 2	61.8 (51.0 - 70.2)	
Pfizer -3 to 4 months post dose 2	59.3 (52.1 - 65.4)	56.0 (16.7 - 76.8)
Pfizer -5 to 6 months post dose 2	55.2 (46.4 - 62.6)	43.9 (20.1 - 60.6)
Pfizer -7 to 8 months post dose 2	65.0 (35.4 - 81.0)	28.8 (10.6 - 43.3)
Pfizer - 9 months post dose 2		
Pfizer - 0 to 13 days post dose 3		
Pfizer - 14 to 27 days post dose 3		
Pfizer -1 to 2 months post dose 3	75.8 (57.4 - 86.3)	66.4 (51.0 - 76.9)
Pfizer -3 to 4 months post dose 3		31.8 (7.9 - 49.4)
Pfizer -5 to 6 months post dose 3		
Pfizer -7 to 8 months post dose 3		
Pfizer -9 months post dose 3		

**Vaccine effectiveness estimates are not provided where p>0.05 for odds ratio of vaccination from the test-negative case-control design, if there are no test volumes or if there are fewer than 10 admissions observed for the estimate. Vaccine effectiveness estimates have not been adjusted for multiplicity.*

Table S8: Vaccine effectiveness estimates amongst population subgroups for 15 November 2021-24 June 2022 ("proxy omicron period (BA1/BA2/BA4/BA5")

	Duration since last dose					
VE (95% CI)	**14-27 days**	**1- 2 months**	**3-4 months**	**5-6 months**	**7-8 months**	**9 + months**
	18-29 years old					
2 doses		66.9 (50.2 - 78.0)	46.9 (17.4 - 65.8)			
3 doses						
	30-39 years old					
2 doses		54.3 (38.9 - 65.9)	48.9 (31.8 - 61.8)			
3 doses						
	40-49 years old					
2 doses		51.5 (33.4 - 64.6)	44.6 (29.5 - 56.4)			
3 doses						
	50-59 years old					
2 doses		71.9 (57.3 - 81.5)	46.1 (32.7 - 56.8)	43.4 (24.7 - 57.4)		
3 doses		66.0 (38.3 - 81.3)				
	60-69 years old					
2 doses		63.2 (36.4 - 78.7)	59.6 (48.4 - 68.4)	45.6 (33.1 - 55.7)	40.2 (20.9 - 54.8)	
3 doses		60.4 (41.8 - 73.1)				

	Duration since last dose					
VE (95% CI)	**14-27 days**	**1- 2 months**	**3-4 months**	**5-6 months**	**7-8 months**	**9 + months**
	70-79 years old					
2 doses		78.3 (59.5 - 88.4)	54.4 (42.5 - 63.8)	54.2 (44.7 - 62.0)	42.2 (25.7 - 55.0)	26.9 (6.2 - 43.1)
3 doses	77.8 (58.2 - 88.2)	76.6 (67.4 - 83.2)	64.8 (51.4 - 74.5)			
	80+ years old					
2 doses			77.5 (51.7 - 89.5)	55.9 (41.2 - 66.9)	47.3 (33.9 - 57.9)	43.2 (22.0 - 58.6)
3 doses		68.0 (38.0 - 83.5)	68.5 (55.1 - 77.8)	57.5 (41.3 - 69.2)		
	No COVID19 risk factors					
2 doses		65.1 (55.0 - 73.0)	60.2 (51.8 - 67.0)	39.6 (27.0 - 50.0)	27.9 (10.9 - 41.7)	
3 doses		76.0 (61.3 - 85.1)				
	1 COVID19 risk factor					
2 doses		40.9 (21.9 - 55.3)	54.0 (44.5 - 61.8)	44.1 (32.7 - 53.6)		
3 doses		72.0 (57.7 - 81.5)	46.6 (15.5 - 66.2)			
	2 COVID19 risk factors					
2 doses		64.5 (47.8 - 75.9)	54.5 (43.7 - 63.1)	41.4 (29.1 - 51.5)	38.8 (20.4 - 52.9)	
3 doses	60.5 (26.6 - 78.7)	61.3 (46.0 - 72.3)	49.3 (24.9 - 65.8)			
	3+ COVID19 risk factors					
2 doses		68.9 (55.9 - 78.1)	46.5 (35.9 - 55.4)	42.5 (32.2 - 51.2)	30.0 (13.3 - 43.6)	
3 doses	78.6 (58.8 - 88.9)	62.4 (49.1 - 72.2)	49.5 (29.0 - 64.0)			

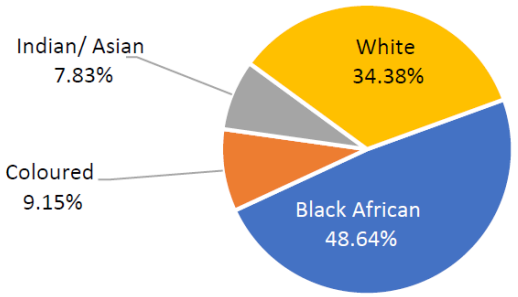
**Vaccine effectiveness estimates are not provided where p>0.05 for odds ratio of vaccination from the test-negative case-control design, if there are no test volumes or if there are fewer than 10 admissions observed for the estimate. Vaccine effectiveness estimates have not been adjusted for multiplicity.*

Table S9: Representativeness of Study Participants.

Category	Example
Disease, problem, or condition under investigation	Vaccine effectiveness against COVID19 hospital admissions in South Africa's Omicron driven fourth wave
Special considerations related to	
Sex	Males are at higher risk of COVID19 admission
Age	The elderly are at higher risk of severe COVID19
Race or ethnic group	This data is not collected by the medical scheme.
Overall representativeness of this study	The study population exhibited the expected male and female ratios of the general population. The age distribution of the population studied is older than the South African public. No race or ethnic group was excluded from the analysis and medical scheme beneficiaries include both blue-collar workers (e.g. mining and retail employees) and white-collar workers (e.g. banking employees and other professionals). All races and ethnic groups are expected to be reasonably represented in the study although these details are not routinely collected by the managed care organization. According to data from StatsSA 2019 general household survey, which was presented to the Parliamentary Portfolio Committee on Health by the Council for Medical Schemes (CMS) on 29 August 2019, Black Africans comprise the largest group of medical scheme members, with slightly less than half of medical scheme beneficiaries being black Africans. The second largest group is white beneficiaries, with slightly more than one third of beneficiaries, followed respectively by colored and Indian/Asian beneficiaries. Overall 64.6% of medical scheme beneficiaries are classified as black (Figure 2). Compared to national figures whites and Indians are overrepresented whilst black African and colored persons are underrepresented (80.7%, 8.8%, 2.6% and 7.5% of the population are black African, colored, Indian/Asian and white, respectively. Source: StatsSA 2019 mid-year population estimates).

Category	Example

Figure 2: Racial composition of medical scheme beneficiaries (2018)



Source: StatsSA (2018).

**The following list of comorbidities (presented in alphabetical order) has been adapted from the Prescribed Minimum Benefits Chronic Disease List (CDL) and the Centers for Disease Control and Prevention (CDC) list of conditions associated with increased risk of severe COVID-19 (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html).

Number	Category	Conditions
1	Cancer	• Cancer
2	Cardiovascular disease	• Cardiac failure • Cardiomyopathy • Coronary artery disease • Dysrhythmias • Peripheral arterial disease • Cerebrovascular disease (including stroke)
3	Chronic renal disease	• Chronic renal disease
4	Chronic respiratory disease	• Asthma • COPD • Bronchiectasis
5	Diabetes mellitus	• Diabetes Mellitus 1 • Diabetes Mellitus 2
6	HIV	• HIV
7	Hypertension	• Hypertension
8	Liver disease	• Alcoholic liver disease • Fatty liver disease • Cirrhosis
9	Neurological disorders	• Epilepsy • Parkinson's disease • Dementia (any cause, including Alzheimer's disease)
10	Overweight / obesity	• BMI >25
11	Severe mental disorders	• Bipolar mood disorder • Schizophrenia
12	Solid organ transplant	• History of Kidney, liver, heart, or lung transplant

References

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