Supplementary Appendix

Supplement to: Collie S, Champion J, Moultrie H, et al. Effectiveness of BNT162b2 vaccine against omicron variant in South Africa. N Engl J Med. DOI: 10.1056/NEJMc2119270

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

Supplement

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1. Methods

We applied a test-negative design to estimate vaccine effectiveness, across two distinct time periods: 15 November – 7 December 2021 in South Africa, which we dubbed a proxy for Omicron variant dominance, against VE estimates between 1 September-30 October 2021 for fully vaccinated members, when the Delta variant was dominant.

Data

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:2020/03/01-2020/10/31, Beta:2020/11/01-2021/05/16, and Delta: 2021/05/17-2021/10/31), and geographic region (province) [Supplementary table 3].

Vaccine effectiveness estimates were obtained from the following formula: 1- odds of COVID19 admission amongst the 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:

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

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

Test negative case control studies have been deemed powerful 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 predicated on the assumption 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 5). 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 is predicated that test results are assessed on a symptomatic population, to avoid bias arising due to a different testing propensity amongst those vaccinated and controls. COVID19 PCR tests are funded from medical scheme benefits on referral from a clinician, and hence test results are most likely to be available for a symptomatic population. Furthermore, testing for travel purposes, is not funded from medical scheme benefits.

Vaccination status was analyzed in the following categories (not vaccinated; 0-3, 4-6, 7-9, 10-13, 14-20, 21-27, 28 days onwards since dose one vaccination; 0-6, 7-13, and 14+ since dose two vaccination for BNT162b2 recipients and other vaccine recipients. Vaccine recipients were classified as other based on a match with the national Electronic Vaccination Data System as at 25 August 2021. We were unable to ascertain vaccine type nor an update from the Department of Health of clients vaccinated in the public sector since.

Therefore, VE estimates provided should be viewed as conservative as unvaccinated controls may inadvertently include vaccinated individuals. Given, the 42 Pfizer dose schedule, and the number of Discovery clients accessing vaccination in public sector sites prior to 25 August 2021, we estimate no more than 10% misclassification error of unvaccinated controls.

Data exclusions rules applied were consistent with those published by Bernal and colleagues[1]:

- Negative tests with 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 with more than two vaccine doses were excluded. During the analysis period, booster doses were not available to the South African public.

Three sensitivity analysis were performed to confirm veracity of VE estimates in the proxy Omicron period:

- First, RT-PCR tests with S-Gene Target Failure were used to detect omicron infections;
- Secondly only COVID19 PCR results within the Gauteng province were analyzed, given the geographical concentration of the Omicron variant over the study period;
- Third, limiting PCR test results limited to the admitted population (e.g. respiratory medical admissions), the latter a proxy for identifying tests amongst a symptomatic population

Each of the mean estimates, including their associated standard errors from each sensitivity analysis, were compared to the mean estimate from the Proxy Omicron period, accounting for its standard error, using the two sample t-test and a p-value<0.05 to reject the null hypothesis, where the null hypothesis is: H_0: $u_{omicron=}\ u_{sensitivity}$

Calculations were performed using R version 4.1.1

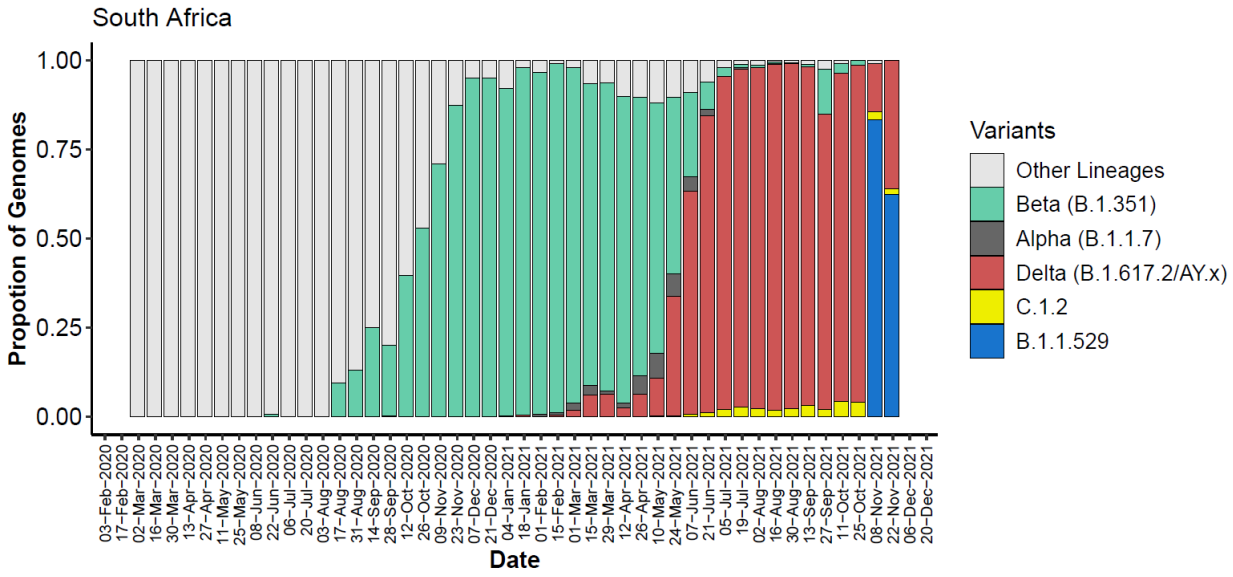
2. References

1. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study; BMJ 2021;373:n1088

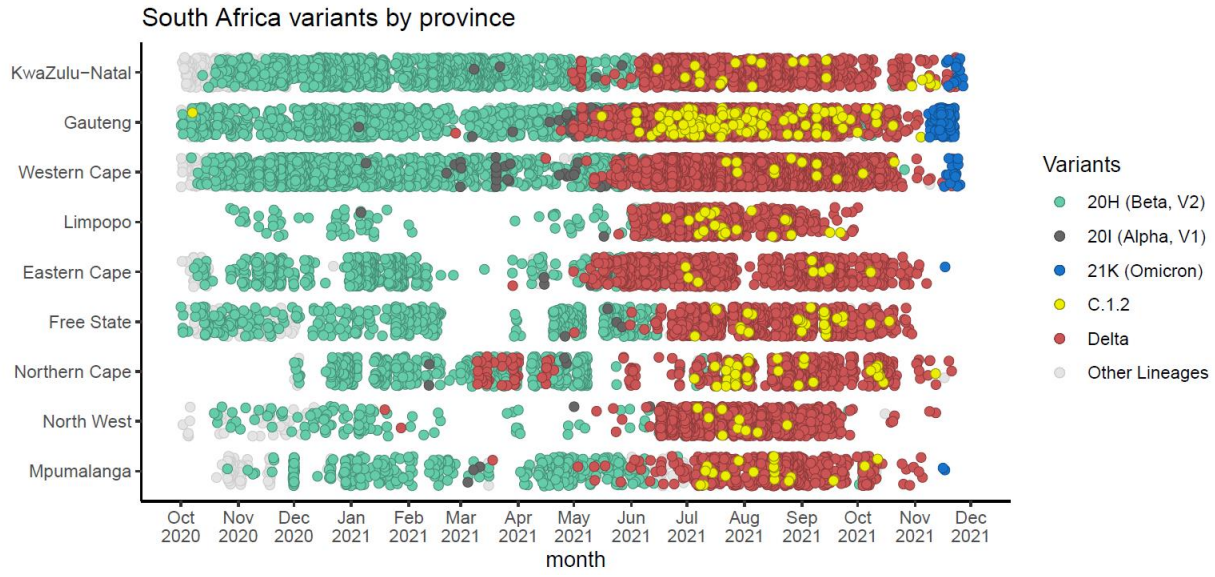
2. Chua H, Feng S, Lewnard JA, et al. The Use of Test-negative Controls to Monitor Vaccine Effectiveness: A Systematic Review of Methodology. Epidemiology. 2020;31(1):43-64. doi:10.1097/EDE.0000000000001116

3. World Health Organization. Design of vaccine efficacy trials to be used during public health emergencies—points of considerations and key principles. 2020. https://www.who.int/docs/default-source/blue-print/working-group-for-vaccine-evaluation-(4th-consultation)/ap1-guidelines-online-consultation.pdf

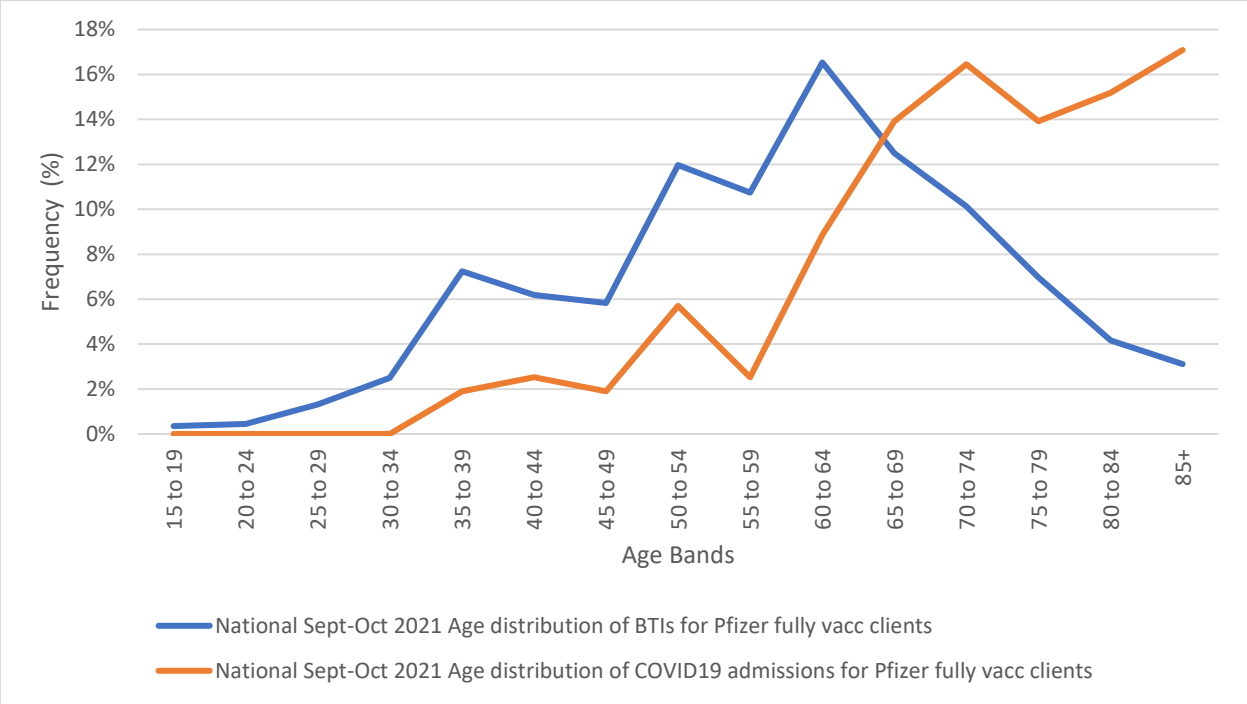
Supplementary figure 1: Genomic sequences by variant type in South Africa by calendar date (Source: Network for Genomic Surveillance in South Africa)



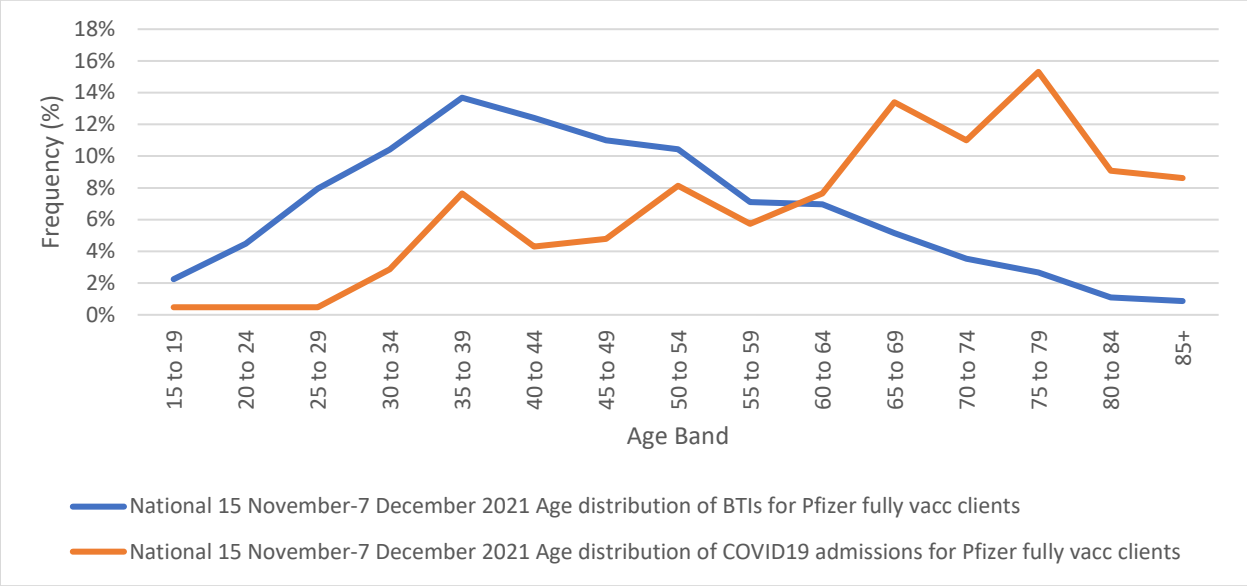
Supplementary figure 2: Genomic sequences by variant type by province in South Africa by calendar date (Source: Network for Genomic Surveillance in South Africa)



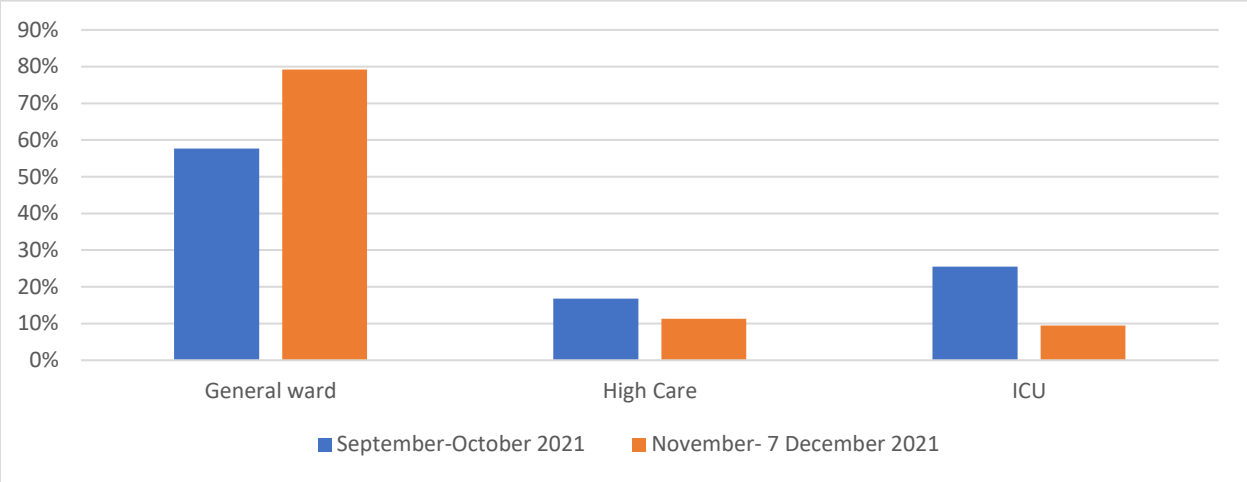
Supplementary figure 3: Frequency distribution (%) of breakthrough infections (BTIs) for Pfizer fully vaccinated Discovery clients vs. percentage frequency distribution of COVID19 admissions for Pfizer fully vaccinated Discovery clients between 1 September 2021-and 31 October 2021 by age band.



Supplementary figure 4: Frequency distribution (%) of breakthrough infections (BTIs) for Pfizer fully vaccinated Discovery clients vs percentage frequency distribution of COVID19 admissions for Pfizer fully vaccinated Discovery clients between 1 November 2021-and 7 December 2021 (proxy Omicron period) by age band.



Supplementary figure 5: Distribution by ward setting for BTI COVID19 admissions for fully Pfizer vaccinated Discovery clients



Supplementary table 1: Total COVID-19 tests in study period

	Number of test (%)
Total Tests from 1 September – 7 December 2021	**259,193 (100.0)**
Negative test within 21 days of positive	1,594 (0.6)
Negative test in the prior 7 days of another negative test	7,352 (2.8)
Prior positive test within 6 weeks	1,258 (0.5)
Greater than 2 vaccine doses received	266 (0.1)
Result missing	299 (0.1)
Age less than 18	35,906 (13.9)
Not chosen as 3 random tests	908 (0.4)
Included in study	**211,610 (81.6)**
01 September - 31 October 2021	133,437 (51.5)
15 November - 7 December 2021 – omicron proxy period	78,173 (30.2)
Sensitivity one: SGTF positive- Lancet Laboratories	34,923 (13.5)
Sensitivity two: Gauteng	42,655 (16.5)
Sensitivity three: Symptomatic admitted population	6,243 (2.4)

Supplementary table 2: Cumulative distribution of time to admission since PCR collection date September-October 2021

Time to admission since PCR collection date Oct/Nov (days)	Not vaccinated cumulative distribution	Vaccinated Cumulative Distribution
0	65.9%	57.9%
1	72.6%	70.7%
2	78.4%	82.6%
3	81.2%	84.7%
4	84.4%	86.8%
5	87.3%	89.1%
6	89.9%	91.2%
7	92.3%	92.5%
8	93.8%	93.9%
9	96.9%	95.3%
10+	100.00%	100.00%

Data was extracted from Discovery data systems on 9 December 2021. This implies that 80% of COVID19 related admissions for cases registered on 7 December 2021 have been included amongst both the vaccinated and unvaccinated population.

Supplementary table 3: Distribution by data by confounders used in analysis

(n,%)	01 October-September 2021			15 November-7 December 2021		
0	Number of tests	Number of positive COVID19 tests	Number of COVID19 admissions	Number of tests	Number of positive COVID19 tests	Number of COVID19 admissions
Age (in years)						
18-29	20,171 (15.1)	1,706 (19.9)	54 (5.8)	13,340 (17.1)	4,407 (23.1)	62 (14.5)
30-39	35,769 (26.8)	2,428 (28.3)	146 (15.8)	21,735 (27.8)	6,341 (33.3)	104 (24.2)
40-49	24,615 (18.4)	1,947 (22.7)	189 (20.4)	15,755 (20.2)	4,293 (22.5)	66 (15.4)
50-59	18,712 (14.0)	1,192 (13.9)	171 (18.5)	10,923 (14.0)	2,231 (11.7)	60 (14.0)
60-69	16,300 (12.2)	659 (7.7)	152 (16.4)	8,279 (10.6)	1,114 (5.8)	50 (11.7)
70-79	12,553 (9.4)	424 (4.9)	125 (13.5)	5,731 (7.3)	507 (2.7)	53 (12.4)
80+	5,317 (4.0)	213 (2.5)	88 (9.5)	2,410 (3.1)	177 (0.9)	34 (7.9)
Sex						
Male	54,255 (40.7)	3,744 (43.7)	461 (49.8)	32,031 (41.0)	8,166 (42.8)	174 (40.6)
Female	79,182 (59.3)	4,825 (56.3)	464 (50.2)	46,142 (59.0)	10,904 (57.2)	255 (59.4)
Number of CDC risk factors**						
0	71,344 (53.5)	5,265 (61.4)	318 (34.4)	45,955 (58.8)	12,910 (67.7)	194 (45.2)
1	36,853 (27.6)	2,131 (24.9)	291 (31.5)	20,966 (26.8)	4,607 (24.2)	125 (29.1)
2	16,987 (12.7)	828 (9.7)	195 (21.1)	8,098 (10.4)	1,229 (6.4)	70 (16.3)
3+	8,253 (6.2)	345 (4.0)	121 (13.1)	3,154 (4.0)	324 (1.7)	40 (9.3)
Calendar week						
35	13,349 (10.0)	2,039 (23.8)	199 (21.5)	0 (0.0)	0 (0.0)	0 (0.0)
36	20,010 (15.0)	2,517 (29.4)	264 (28.5)	0 (0.0)	0 (0.0)	0 (0.0)
37	18,102 (13.6)	1,600 (18.7)	156 (16.9)	0 (0.0)	0 (0.0)	0 (0.0)
38	12,942 (9.7)	741 (8.6)	81 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)
39	15,164 (11.4)	646 (7.5)	75 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)
40	14,177 (10.6)	395 (4.6)	56 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)
41	14,711 (11.0)	329 (3.8)	43 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)
42	12,795 (9.6)	166 (1.9)	28 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
43	12,187 (9.1)	136 (1.6)	23 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
46	0 (0.0)	0 (0.0)	0 (0.0)	13,314 (17.0)	351 (1.8)	25 (5.8)
47	0 (0.0)	0 (0.0)	0 (0.0)	15,982 (20.4)	1,842 (9.7)	65 (15.2)
48	0 (0.0)	0 (0.0)	0 (0.0)	32,436 (41.5)	10,520 (55.2)	231 (53.8)
Period of last documented prior infection						
None	117,510 (88.1)	8,238 (96.1)	890 (96.2)	65,292 (83.5)	16,846 (88.3)	390 (90.9)

D614G (2020/03/01-2020/10/31)	4,741 (3.6)	103 (1.2)	17 (1.8)	2,688 (3.4)	613 (3.2)	11 (2.6)
Beta (2020/11/01-2021/05/16)	6,650 (5.0)	142 (1.7)	11 (1.2)	3,787 (4.8)	658 (3.5)	11 (2.6)
Delta (2021/05/17-2021/10/31)	4,536 (3.4)	86 (1.0)	7 (0.8)	6,406 (8.2)	953 (5.0)	17 (4.0)
Province						
Eastern Cape	7,251 (5.4)	908 (10.6)	72 (7.8)	2,295 (2.9)	325 (1.7)	8 (1.9)
Free State	5,712 (4.3)	600 (7.0)	95 (10.3)	2,359 (3.0)	356 (1.9)	15 (3.5)
Gauteng	55,397 (41.5)	1,795 (20.9)	170 (18.4)	42,655 (54.6)	13,348 (70.0)	246 (57.3)
Kwazulu Natal	22,653 (17.0)	1,673 (19.5)	255 (27.6)	10,203 (13.1)	1,498 (7.9)	75 (17.5)
Limpopo	2,126 (1.6)	101 (1.2)	16 (1.7)	1,415 (1.8)	493 (2.6)	11 (2.6)
Mpumalanga	4,837 (3.6)	314 (3.7)	40 (4.3)	2,531 (3.2)	668 (3.5)	19 (4.4)
North West	4,515 (3.4)	248 (2.9)	37 (4.0)	2,338 (3.0)	544 (2.9)	14 (3.3)
Northern Cape	2,295 (1.7)	282 (3.3)	29 (3.1)	904 (1.2)	81 (0.4)	3 (0.7)
Western Cape	28,020 (21.0)	2,607 (30.4)	211 (22.8)	13,000 (16.6)	1,588 (8.3)	36 (8.4)
Not allocated	631 (0.5)	41 (0.5)	0 (0.0)	473 (0.6)	169 (0.9)	2 (0.5)

Supplementary table 4: Sensitivity Analysis

(n,%)	Sensitivity one: SGTF positive-Lancet Laboratories			Sensitivity two: Gauteng			Sensitivity three: Symptomatic admitted population		
	Number of tests	Number of positive COVID19 tests	Number of COVID19 admissions	Number of tests	Number of positive COVID19 tests	Number of COVID19 admissions	Number of tests	Number of positive COVID19 tests	Number of COVID19 admissions
Not Vaccinated	12,548 (35.9)	3,345 (44.6)	50 (53.2)	14,220 (33.3)	5,478 (41.0)	117 (47.6)	2,034 (32.6)	252 (52.2)	220 (51.8)
Pfizer dose one	2,887 (8.3)	572 (7.6)	9 (9.6)	3,637 (8.5)	1,087 (8.1)	27 (11.0)	421 (6.7)	35 (7.2)	33 (7.8)
Pfizer <14 days post dose two	291 (0.8)	31 (0.4)	0 (0.0)	382 (0.9)	79 (0.6)	0 (0.0)	33 (0.5)	0 (0.0)	0 (0.0)
Pfizer >=14 days post dose two	13,682 (39.2)	2,337 (31.2)	27 (28.7)	17,789 (41.7)	4,478 (33.5)	72 (29.3)	2,935 (47.0)	132 (27.3)	120 (28.2)
Other vaccine* type	5,515 (15.8)	1,214 (16.2)	8 (8.5)	6,627 (15.5)	2,226 (16.7)	30 (12.2)	820 (13.1)	64 (13.3)	52 (12.2)
Total	34,923 (100.0)	7,499 (100.0)	94 (100.0)	42,655 (100.0)	13,348 (100.0)	246 (100.0)	6,243 (100.0)	483 (100.0)	425 (100.0)

**Based on a match with the national Electronic Vaccination Data System as at 25 August 2021. We were unable to ascertain vaccine type nor an update from the Department of Health of clients vaccinated in the public sector since. Therefore, VE estimates provided should be viewed as conservative as unvaccinated controls may inadvertently include vaccinated individuals. Given, the 42 Pfizer dose schedule, and the number of Discovery clients accessing vaccination in public sector sites prior to 25 August 2021, we estimate no more than 10% misclassification error of unvaccinated controls.*

Supplementary table 5: Discovery Health Population: positive and negative controls

	Negative control distribution 01 September - 31 October 2021	Positive and Negative distribution 01 September - 31 October 2021	Negative control distribution 15 November - 7 December 2021	Positive and Negative distribution -15 November-7 December 2021	All Discovery Health administered scheme adult population – 01 September 2021	All Discovery Health administered scheme adult population -7 December 2021
Not vaccinated	38.6%	40.0%	31.2%	33.7%	43.3%	38.9%
Pfizer dose one	12.5%	12.7%	8.0%	7.9%	13.5%	7.5%
Pfizer less than 4 days post dose two	4.0%	3.9%	0.9%	0.8%	2.6%	1.4%
Pfizer greater than and equal to 14 days post dose two	30.0%	28.6%	44.1%	41.4%	25.6%	36.8%
Other vaccine type	14.9%	14.8%	15.9%	16.2%	15.0%	15.4%

Supplementary Table 6: 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

Number	Category	Conditions
12	Solid organ transplant	• History of Kidney, liver, heart, or lung transplant