

**Title: Outcomes of laboratory-confirmed SARS-CoV-2 infection during resurgence driven by Omicron lineages BA.4 and BA.5 compared with previous waves in the Western Cape Province, South Africa**

**Authors\***

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## Abstract

**Objective:** We aimed to compare clinical severity of Omicron BA.4/BA.5 infection with BA.1 and earlier variant infections among laboratory-confirmed SARS-CoV-2 cases in the Western Cape, South Africa, using timing of infection to infer the lineage/variant causing infection.

**Methods:** We included public sector patients aged  $\geq 20$  years with laboratory-confirmed COVID-19 between 1-21 May 2022 (BA.4/BA.5 wave) and equivalent prior wave periods. We compared the risk between waves of (i) death and (ii) severe hospitalization/death (all within 21 days of diagnosis) using Cox regression adjusted for demographics, comorbidities, admission pressure, vaccination and prior infection.

**Results:** Among 3,793 patients from the BA.4/BA.5 wave and 190,836 patients from previous waves the risk of severe hospitalization/death was similar in the BA.4/BA.5 and BA.1 waves (adjusted hazard ratio [aHR] 1.12; 95% confidence interval [CI] 0.93; 1.34). Both Omicron waves had lower risk of severe outcomes than previous waves. Prior infection (aHR 0.29, 95% CI 0.24; 0.36) and vaccination (aHR 0.17; 95% CI 0.07; 0.40 for boosted vs. no vaccine) were protective.

**Conclusion:** Disease severity was similar amongst diagnosed COVID-19 cases in the BA.4/BA.5 and BA.1 periods in the context of growing immunity against SARS-CoV-2 due to prior infection and vaccination, both of which were strongly protective.

## Background

The Omicron SARS-CoV-2 variant of concern (VOC) has been dominant globally since November 2021, with several lineages causing surges in infections (Iketani et al., 2022, Tegally et al., 2022, Viana et al., 2022). South Africa experienced an initial large BA.1 infection surge from November 2021 to January 2022. BA.1 was then replaced by BA.2 but with no increase in cases numbers, and this was followed by a BA.4/BA.5 infection surge between April and June 2022 (Tegally et al., 2022, Viana et al., 2022). The combination of mutations in BA.4/BA.5 appear to confer a growth advantage over BA.2, as well as immune escape from vaccine-derived and BA.1 elicited antibodies (Khan et al., 2022, Tegally et al., 2022). A growing number of BA.4 and BA.5 infections are now being reported globally (Callaway, 2022, UK Health Security Agency, 2022).

We therefore compared outcomes of laboratory-confirmed SARS-CoV-2 infections during the recent resurgence (proxy for BA.4/ BA.5 infection) with outcomes during each of the four previous waves in South Africa, each of which were caused by a different variant or lineage, using data on patients with laboratory-confirmed SARS-CoV-2 infection aged  $\geq 20$  years using public sector services in the Western Cape Province, South Africa.

## Methods:

We conducted a cohort study using de-identified data from the Western Cape Provincial Health Data Centre (WCPHDC) of public sector patients aged  $\geq 20$  years with a laboratory confirmed COVID-19 diagnosis (positive SARS-CoV-2 PCR or antigen test). The Western Cape has nearly 7 million inhabitants, of whom approximately 75% use public sector health services (Western Cape Department of Health, 2020). The WCPHDC and methods for this study have previously been described in detail (Boulle et al., 2019, Davies et al., 2022, Hussey et al., 2022, Western Cape Department of Health in collaboration with the National

Institute for Communicable Diseases, 2020). Briefly, for this analysis, waves of infection were defined as starting and ending when the 7-day moving average of public sector COVID-19 hospital admissions exceeded and dropped below 5 and 12 per million population respectively. We included cases diagnosed from seven days before the wave start to seven days before the wave end date to account for the lag between infection/first symptoms and hospitalization. We thus included data on cases diagnosed from 1-21 May 2022 for the BA.4/BA.5 wave, with follow-up through to 11 June 2022, corresponding to the period when BA.4/BA.5 dominated in the province (Network for Genomic Surveillance in South Africa, 2022).

We used Cox regression adjusted for age, sex, geographic location, comorbidities, service pressure (number of weekly admissions in the health district) at time of diagnosis, prior diagnosed infection ( $\geq 1$  laboratory confirmed SARS-CoV-2 diagnosis  $\geq 90$  days previously) and SARS-CoV-2 vaccination to assess differences in the following COVID-19 outcomes between waves driven by different variants: (i) death and (ii) death or severe hospitalization (admission to intensive care or mechanical ventilation or oral/intravenous steroid prescription). We only included outcomes within 21 days of COVID-19 diagnosis for comparable ascertainment across all waves. All deaths within 21 days of a COVID-19 diagnosis were included unless a clear non-COVID-19 cause of death was recorded. For patients with recorded South African national identity numbers, data are linked to the South African vital registry to identify deaths not recorded in the WCPHDC. Vaccination data was obtained by linking the South African national identifier to the Electronic Vaccine Data System which records all vaccines administered in the country. The only vaccines available in South Africa to date are BNT162b and Ad26.COVS.2.S. Vaccination status was categorized as either (i) “boosted” (three or more homologous or heterologous doses of any vaccine), (ii) “two doses” (two doses of any vaccine) or (iii) “single dose” (single dose of Ad26.COVS.2.S), as the latter is considered complete primary vaccination in South Africa.

The study was approved by the University of Cape Town and Stellenbosch University Health Research Ethics Committees and Western Cape Government: Health. Individual informed consent requirement was waived for this secondary analysis of de-identified data.

## Results

We included 3,793 patients diagnosed in the BA.4/BA.5 wave and 27,614 (BA.1), 68,715 (Delta), 54,268 (Beta) and 40,204 (ancestral) in waves driven by previous variants (Table 1). The proportion with prior diagnosed infection was substantially higher in the BA.4/BA.5 (18.9%) and BA.1 (11.9%) waves compared to previous waves (<3%). In the BA.4/BA.5 wave, 12.9% of COVID-19 cases had received “single dose” Ad26.COV2.S vaccination, 36.1% had received “two doses” and 6.7% were “boosted” vaccinees.

The adjusted hazard of severe hospitalization or death in the BA.4/BA.5 wave was similar to the BA.1 wave (adjusted hazard ratio [aHR] 1.12; 95% confidence interval [CI]: 0.93; 1.34) (Table 2). Both Omicron-driven waves had lower hazards of severe hospitalization or death than previous waves (Table 2). Prior diagnosed infection was strongly protective against severe hospitalization or death (aHR 0.29; 95% CI 0.24; 0.36) as was vaccination with aHR (95% CI) of 0.17 (0.07; 0.40); 0.37 (0.33; 0.42) and 0.26 (0.21; 0.32) for “boosted”, “two doses” and “single dose”, respectively. In a model not adjusting for vaccination and prior diagnosed infection, the hazard of severe hospitalization or death in the BA.4/BA.5 vs. BA.1 waves was reduced compared to the fully adjusted model (aHR 0.90; 95% CI: 0.75; 1.08). In an analysis restricted to the BA.4/BA.5 period, prior diagnosed infection remained strongly protective against severe hospitalization or death (aHR 0.23; 95% CI 0.10; 0.52) as did vaccination (aHR [95% CI]: 0.20 (0.08; 0.49); 0.39 (0.25; 0.59) and 0.51 (0.27; 0.99) for “boosted”, “two doses” and “single dose”, respectively. Results were all similar when examining the outcome of death alone.

## Discussion

Using the period of diagnosis as a proxy for being infected with different Omicron lineages in the Western Cape, we found no difference in the risk of severe COVID-19 hospitalization or death during the BA.4/BA.5 period compared to the BA.1 period, both of which had better outcomes than previous waves. Strong protection against severe COVID-19 conferred by prior infection and vaccination was retained in the BA.4/BA.5 wave, with three homologous doses of Ad26.COV2.S or BNT162b2 or a heterologous combination of these providing 83% protection (95% CI 60; 93%) against severe COVID-19 hospitalization or death amongst laboratory-confirmed cases.

A study in animals recently suggested that BA.4/BA.5 may be more pathogenic than BA.2 (Kimura et al., 2022). Although we did not compare BA.4/BA.5 with BA.2 directly as BA.2 did not cause a distinguishable surge in infections in the Western Cape, disease severity of BA.2 and BA.1 are similar (Lewnard et al., 2022) and we found no evidence of worse clinical outcomes with BA.4/BA.5 compared to BA.1. Nonetheless, our findings need to be interpreted in the context of South African SARS-CoV-2 epidemiology with progressively increasing seroprevalence due to prior infection (mostly undiagnosed) and/or vaccination (Bingham et al., 2022, Madhi et al., 2022, Sun et al., 2022). For example, among blood donors, after the BA.1 wave the estimated national prevalence of anti-nucleocapsid antibodies was 87% (indicating previous infection) with a further 10% having anti-spike antibodies only (suggesting vaccination without prior infection) (Bingham et al., 2022). Indeed, our finding that the aHR shifted towards a lower risk of severe outcomes during BA.4/BA.5 vs. BA.1 in models not accounting for vaccination and prior diagnosed infection, suggests that the observed continued ecologic decoupling of COVID-19 cases and severe outcomes is at least partly due to growing protection against severe disease from both prior infection and vaccination. With the progression of the SARS-CoV-2 pandemic globally, it is increasingly difficult to determine the clinical severity of any variant in a completely naïve



individual. However, for health service planning this is less relevant than the real-world effect in populations with varying degrees of immune protection (Mefsin et al., 2022). For example, although we showed similar risk of severe hospitalization or death in the BA.4/BA.5 and BA.1 waves when adjusted for vaccination and prior diagnosed infection, the actual burden of admissions and deaths was much lower in the BA.4/BA.5 waves, with the peak 7-day moving average of admissions and deaths being 222 and 36 in the BA.1 wave vs. 66 and 9 in the BA.4/BA.5 wave. The ability to use routine data to rapidly assess the relative severity of waves caused by different lineages and variants adjusted for comorbidities, vaccination and prior infection has been especially valuable for local health service planning (Davies et al., 2022).

To our knowledge, this is one of the first comparisons of clinical severity of BA.4/BA.5 infections with previous variants with relatively complete adjustment for comorbidities and vaccination among all diagnosed cases. Nonetheless, this type of data and analysis have several limitations which have been described in detail previously (Davies et al., 2022). These include using the time of infection as a proxy for the variant causing infection rather than actual genomic sequencing or PCR test proxies (Wolter et al., 2022) which would be more accurate and overcome challenges with comparing disease severity across waves due to differences in testing practices, treatment availability and health service pressures. Notably, testing in the BA.4/BA.5 wave was at the lowest levels since the start of the pandemic with less testing of patients with milder disease, hence we may have over-estimated disease severity in this wave. With routine data we were unable to distinguish between severe hospitalizations and deaths where the diagnosis of COVID-19 may have been incidental or contributory rather than causal, and had incomplete ascertainment of key covariates especially prior diagnosed infection due to substantial missed diagnoses, vaccinations received outside of the province or without submitting a South African identity number and

undiagnosed comorbidities as we can only adjust for those algorithmically identified in the WCPHDC.

In conclusion, we found similar disease severity amongst diagnosed COVID-19 cases in the BA.4/BA.5 and BA.1 periods in the context of growing immunity against SARS-CoV-2 with strong protection against severe outcomes conferred by prior infection and vaccination, especially if boosted. Ensuring that individuals at high risk of severe COVID-19 outcomes have at least three vaccine doses remains a key strategy for limiting the public health impact of further COVID-19 waves.

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### **Conflict of interest**

All authors declare that they have no conflicts of interest.

### **Ethical approval statement**

The study was approved by the University of Cape Town and Stellenbosch University Health Research Ethics Committees and Western Cape Government: Health. Individual informed consent requirement was waived for this secondary analysis of de-identified data.

Table 1: Characteristics and outcomes of COVID-19 cases included from each infection period in the Western Cape

	<b>Ancestral wave</b> 25 Apr to 22 Jul 2020 <sup>a</sup> (n=40,204)	<b>Beta wave</b> 3 Nov 2020 to 22 Jan 2021 <sup>a</sup> (n=54,268)	<b>Delta wave</b> 30 May to 10 Sep 2021 <sup>a</sup> (n=68,750)	<b>BA.1 wave</b> 27 Nov 2021 to 12 Jan 2022 <sup>a</sup> (n=27,614)	<b>BA.4/BA.5 wave</b> 1 May to 21 May 2022 <sup>a</sup> (n=3,793)
<b>Male sex</b>	13,380 (33.3%)	19,083 (35.2%)	25,948 (37.7%)	9,630 (34.9%)	1,327 (35.0%)
<b>Age</b>					
<b>20-39 years</b>	18,720 (46.6%)	21,839 (40.2%)	29,720 (43.2%)	13,944 (50.5%)	1,783 (47.0%)
<b>40-49 years</b>	8,280 (20.6%)	10,594 (19.5%)	14,163 (20.6%)	4,905 (17.8%)	767 (20.2%)
<b>50-59 years</b>	6,982 (17.4%)	10,493 (19.3%)	13,294 (19.3%)	4,216 (15.3%)	623 (16.4%)
<b>60-69 years</b>	3,733 (9.3%)	6,929 (12.8%)	6,780 (9.9%)	2,554 (9.3%)	333 (8.8%)
<b>≥70 years</b>	2,489 (6.2%)	4,413 (8.1%)	4,793 (7.0%)	1,995 (7.2%)	287 (7.6%)
<b>Non-communicable diseases</b>					
<b>diabetes</b>	8,265 (20.6%)	11,509 (21.1%)	11,581 (16.9%)	3,627 (13.1%)	406 (10.7%)
<b>hypertension</b>	13,065 (32.5%)	19,070 (35.1%)	21,170 (30.8%)	7,063 (25.6%)	842 (22.2%)
<b>chronic kidney disease</b>	2,013 (5.0%)	2,778 (5.2%)	3,018 (4.4%)	958 (3.5%)	124 (3.3%)
<b>chronic pulmonary disease / asthma</b>	3,099 (7.7%)	4,661 (8.6%)	6,434 (9.4%)	3,040 (11.0%)	411 (10.8%)
<b>Tuberculosis</b>					
<b>previous tuberculosis</b>	2,777 (6.9%)	3,450 (6.4%)	4,850 (7.1%)	2,229 (8.1%)	232 (6.1%)
<b>current tuberculosis</b>	513 (1.3%)	555 (1.0%)	803 (1.2%)	578 (2.1%)	76 (2.0%)
<b>HIV positive</b>	6,203 (15.4%)	5,512 (10.2%)	5,925 (8.6%)	3,298 (11.9%)	307 (8.1%)
<b>Prior diagnosed SARS-CoV-2 infection</b>	0 (0%)	618 (1.1%)	1,798 (2.6%)	3,179 (11.5%)	715 (18.9%)
<b>Vaccination<sup>b</sup></b>					
<b>none</b>	N/A	N/A	63,644 (92.6%)	14,471 (52.4%)	1,535 (40.5%)
<b>single dose Ad26.COVS</b>	N/A	N/A	2,501 (3.6%)	4,069 (14.7%)	488 (12.9%)
<b>single dose BNT162b2</b>	N/A	N/A	2,289 (3.3%)	1,144 (4.1%)	147 (3.9%)
<b>2 doses Ad26.COVS</b>	N/A	N/A	30 (0.04%)	1,127 (4.1%)	298 (7.9%)
<b>2 doses BNT162b2</b>	N/A	N/A	286 (0.4%)	6,763 (24.5%)	1,067 (28.1%)
<b>2 doses Ad26.COVS + BNT162b2</b>	N/A	N/A	N/A	N/A	5 (0.1%)
<b>≥3 doses Ad26.COVS</b>	N/A	N/A	N/A	36 (0.1%)	38 (1.0%)
<b>≥3 doses BNT162b2</b>	N/A	N/A	N/A	4 (0.01%)	192 (5.1%)
<b>≥3 doses Ad26.COVS + BNT162b2</b>	N/A	N/A	N/A	N/A	23 (0.6%)
<b>Outcomes within 21 days of diagnosis</b>					
<b>severe admission (not deceased)<sup>c</sup></b>	N/A <sup>c</sup>	1,916 (3.5%)	2,066 (3.0%)	481 (1.7%)	61 (1.6%)
<b>death</b>	2,147 (5.3%)	3,717 (6.9%)	4368 (6.4%)	699 (2.5%)	70 (1.9%)

<sup>a</sup>Date of diagnoses for cases included in each wave. We included cases diagnosed from 7 days prior to the "wave start" to the date of wave end (deemed to occur when 7 day moving average of daily new public sector admissions exceeded 5/million (start) and dropped below 12/million (end) respectively). <sup>b</sup>Vaccination is summarized as vaccine type and number of doses provided diagnosis was ≥28 days after first dose, ≥14 days after second dose, and ≥7 days after third dose; <sup>c</sup>Admission to an intensive care unit, mechanical ventilation or prescription of oral or intravenous steroids; not reported for wave 1 as steroids not widely used until after 16 June 2020. N/A = not applicable

Table 2: Associations between different infection periods and severe COVID-19 outcomes adjusted for patient characteristics, sub-district, vaccination, and prior diagnosed infection using Cox regression.

	Outcome = death not adjusted for vaccination and prior infection		Outcome = death adjusted for vaccination and prior infection		Outcome = severe hospitalization <sup>a</sup> /death not adjusted for vaccination or prior diagnosed infection		Outcome = severe hospitalization <sup>a</sup> /death adjusted for vaccination or prior diagnosed infection	
	Adjusted <sup>b</sup> HR	95% CI	Adjusted HR	95% CI	Adjusted <sup>b</sup> HR	95% CI	Adjusted HR	95% CI
<b>Male sex (vs. female)</b>	1.40	1.34; 1.45	1.40	1.34; 1.45	1.27	1.23; 1.31	1.26	1.22; 1.30
<b>Age (vs. 20-39 years)</b>								
40-49 years	2.54	2.30; 2.81	2.57	2.33; 2.84	2.00	1.87; 2.15	2.04	1.90; 2.19
50-59 years	5.46	4.99; 5.97	5.56	5.08; 6.08	3.42	3.21; 3.65	3.50	3.28; 3.74
60-69 years	12.55	11.47; 13.73	12.88	11.77; 14.10	6.39	5.97; 6.83	6.56	6.13; 7.01
≥70 years	23.19	21.15; 25.43	23.93	21.82; 26.24	10.35	9.65; 11.09	10.65	9.94; 11.42
<b>Comorbidities (vs. comorbidity absent)</b>								
diabetes	2.01	1.92; 2.10	2.01	1.93; 2.10	1.97	1.89; 2.04	1.98	1.91; 2.06
hypertension	1.08	1.03; 1.13	1.07	1.02; 1.12	1.18	1.14; 1.23	1.17	1.13; 1.22
chronic kidney disease	1.90	1.80; 2.00	1.90	1.81; 2.00	1.63	1.56; 1.70	1.63	1.56; 1.70
chronic pulmonary disease / asthma	0.98	0.93; 1.04	0.99	0.93; 1.04	1.18	1.13; 1.23	1.19	1.14; 1.24
previous tuberculosis	1.30	1.20; 1.40	1.28	1.19; 1.38	1.25	1.17; 1.33	1.23	1.16; 1.31
current tuberculosis	2.53	2.20; 2.91	2.44	2.13; 2.81	2.89	2.59; 3.23	2.79	2.50; 3.11
HIV	1.60	1.48; 1.72	1.60	1.49; 1.72	1.54	1.45; 1.64	1.54	1.45; 1.64
<b>Number of admissions in district in week of diagnosis (vs &lt;1/3 of maximum)</b>								
1/3 to <2/3	1.11	1.05; 1.17	1.12	1.06; 1.18	1.03	0.98; 1.08	1.04	0.99; 1.09
≥2/3	1.12	1.05; 1.20	1.13	1.06; 1.21	1.05	0.99; 1.11	1.06	1.00; 1.12
<b>Prior diagnosed SARS CoV-2 infection</b>								
Yes (vs none)			0.51	0.42; 0.63			0.29	0.24; 0.36
<b>Vaccination (vs. None)<sup>c</sup></b>								
single dose Ad26.COVS.2			0.24	0.18; 0.33			0.26	0.21; 0.32
two doses (Ad26.COVS.2 and/or BNT162b2)			0.36	0.31; 0.42			0.37	0.33; 0.42
boosted (≥ 3doses Ad26.COVS.2 and/or BNT162b2)			0.06	0.01; 0.40			0.17	0.07; 0.40
<b>Wave period (dominant variant)</b>								
wave 1 (ancestral)	2.08	1.90; 2.28	1.30	1.17; 1.44	N/A <sup>a</sup>		N/A <sup>a</sup>	
wave 2 (Beta)	2.35	2.16; 2.57	1.47	1.34; 1.62	2.06	1.93; 2.20	1.28	1.20; 1.38
wave 3 (Delta)	2.58	2.37; 2.81	1.75	1.59; 1.92	2.16	2.03; 2.29	1.44	1.35; 1.54
wave 4 (Omicron BA.1)	Ref		Ref		Ref		Ref	
wave 5 (Omicron BA.4/BA.5)	0.93	0.72; 1.20	1.16	0.90; 1.50	0.90	0.75; 1.08	1.12	0.93; 1.34

<sup>a</sup>Admission to an intensive care unit, mechanical ventilation or prescription of oral or intravenous steroids; not reported for wave 1 as steroids not widely used until after 16 June 2020. <sup>b</sup>Adjusted for all variables shown in the table as well as subdistrict/district, but not for vaccination or prior diagnosed infection

<sup>c</sup>Vaccination status is categorized as “single dose” (≥28 days after single dose Ad26.COVS.2), “two doses” (≥14 days after second dose of homologous or heterologous vaccination with Ad26.COVS.2 and/or BNT162b2), and “boosted” (≥7 days after third dose of homologous or heterologous vaccination with Ad26.COVS.2 and/or BNT162b2); HR = hazard ratio; CI = confidence interval; N/A = not applicable

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