Clinical severity of Omicron sub-lineage BA.2 compared to BA.1 in South Africa

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ABSTRACT

Early data indicated that infection with Omicron BA.1 sub-lineage was associated with a lower risk of hospitalisation and severe illness, compared to Delta infection. Recently, the BA.2 sub-lineage has increased in many areas globally. We aimed to assess the severity of BA.2 infections compared to BA.1 in South Africa. We performed data linkages for (i) national COVID-19 case data, (ii) SARS-CoV-2 laboratory test data, and (iii) COVID-19 hospitalisations data, nationally. For cases identified using TaqPath COVID-19 PCR, infections were designated as S-gene target failure (SGTF, proxy for BA.1) or S-gene positive (proxy for BA.2). Disease severity was assessed using multivariable logistic regression models comparing individuals with S-gene positive infection to SGTF-infected individuals diagnosed between 1 December 2021 to 20 January 2022. From week 49 (starting 5 December 2021) through week 4 (ending 29 January 2022), the proportion of S-gene positive infections increased from 3% (931/31,271) to 80% (2,425/3,031). The odds of being admitted to hospital did not differ between individuals with S-gene positive (BA.2 proxy) infection compared to SGTF (BA.1 proxy) infection (adjusted odds ratio (aOR) 0.96, 95% confidence interval (CI) 0.85-1.09). Among hospitalised individuals, after controlling for factors associated with severe disease, the odds of severe disease did not differ for individuals with S-gene positive infection compared to SGTF infection (aOR 0.91, 95%CI 0.68-1.22). These data suggest that while BA.2 may have a competitive advantage over BA.1 in some settings, the clinical profile of illness remains similar.

MAIN TEXT

The Omicron SARS-CoV-2 variant of concern was first reported in South Africa in mid-November 2021. Early data indicated that infection with Omicron (~99% BA.1 sub-lineage during this period) was associated with a lower risk of hospitalisation and lower risk of severe illness, once hospitalised, compared to Delta variant infection.[1] Recently, the BA.2 sub-lineage has increased in many areas globally including South Africa, associated with increases in case numbers in some settings. In South Africa, the BA.2 sub-lineage was first detected on 17 November 2021. From week 49 (starting 5 December 2021), the proportion of BA.2 sub-lineage began to increase, making up 84% (27/32) of all sequenced samples by week 5 (week ending 5 February 2022).[2] Replacement of BA.1 by BA.2 occurred in a period when SARS-CoV-2 case numbers were declining from the fourth wave peak in South Africa and was associated with a brief increase in case numbers in children of school-going age and slowing of the rate of decline compared to previous waves.

Similar to BA.1, BA.2 is associated with substantial loss in neutralising activity in individuals infected with wild-type SARS-CoV-2 or recipients of mRNA vaccines.[3] BA.2 has also been associated with increased transmissibility compared to BA.1.[4] However, data are lacking on the clinical severity of the BA.2 sub-lineage compared to BA.1. We aimed to assess the severity of BA.2 infections compared to BA.1 in South Africa.

Using previously described methods[1], we performed individual-level data linkage for national data from three sources: (i) national COVID-19 case data, (ii) SARS-CoV-2 laboratory test data for public sector laboratories and one large private sector laboratory, and (iii) DATCOV, which is an active surveillance system for COVID-19 hospital admissions in South Africa (including both incidental and attributable admissions). Case and test data were obtained on 29 January 2022, and DATCOV data on 10 February 2022. The BA.1 sub-lineage contains the 69-70 deletion, which is associated with S-gene target failure (SGTF) when tested using the TaqPath™ COVID-19 PCR test (Thermo Fisher Scientific, Waltham, MA, USA). BA.2 lacks this deletion, hence infections with BA.2 are S-gene positive on this assay. In this analysis, restricted to tests performed on the TaqPath™ COVID-19 assay, S-gene positive and S-gene target failure (SGTF) infections were considered proxies for Omicron sub-lineages BA.2 and BA.1, respectively.

Two multivariable logistic regression models were generated to assess risk factors for (i) hospitalisation and (ii) severe disease among hospitalised individuals, comparing S-gene positive infections (proxy for BA.2) to SGTF infections (proxy for BA.1). We controlled for factors associated with hospitalisation (age, sex, presence of co-morbidity, province, healthcare sector and prior SARS-CoV-2 infection) and factors associated with severity (age, presence of co-morbidity, sex, province,

healthcare sector, number of days between the dates of specimen collection and hospital admission, known prior SARS-CoV-2 infection and SARS-CoV-2 vaccination status) in the respective models. Cases were censored to those with a specimen collected before 20 January 2022, to allow for at least three weeks of follow up. Severity analysis was restricted to admissions that had already accumulated outcomes and all patients still in hospital were excluded. Severe disease was defined as a hospitalised patient meeting at least one of the following criteria: admitted to the intensive care unit (ICU), received any level of oxygen treatment, ventilated, received extracorporeal membrane oxygenation (ECMO), experienced acute respiratory distress syndrome and/or died.

From 1 December 2021 through 29 January 2022, 680,555 SARS-CoV-2 infections were reported. From week 49 (starting 5 December 2021) through week 4 (ending 29 January 2022), the proportion of S-gene positive infections increased from 3% (931/31,271) to 80% (2,425/3,031) (Supplementary figure 1). Among 95,470 samples tested using the TaqPath™ COVID-19 PCR assay, 3.6% of individuals with S-gene positive infection (BA.2 proxy) were hospitalised compared to 3.4% with SGTF infection (BA.1 proxy)(Table 1).

On multivariable analysis, after controlling for factors associated with hospitalisation, the odds of being admitted to hospital did not differ between individuals with S-gene positive (BA.2 proxy) infection compared to SGTF (BA.1 proxy) infection (adjusted odds ratio (aOR) 0.96, 95% confidence interval (CI) 0.85-1.09) (Table 1). In addition to geographic factors, hospital admission was associated with female sex (aOR 1.14, 95% CI 1.06-1.22) and young age (<5 years, aOR 7.49, 95% CI 6.02-9.32) and older age (40-59 years, aOR 1.39, 95%CI 1.16-1.66 and ≥60 years, aOR 4.97, 95% CI 4.12-5.94) compared to individuals aged 19-24 years. Individuals in the private healthcare sector were less likely to be admitted to hospital (aOR 0.63, 95% CI 0.58-0.68) compared to those in the public sector.

Among hospitalised individuals diagnosed from 1 December 2021 to 20 January 2022, after controlling for factors associated with severe disease, the odds of severe disease did not differ for individuals with S-gene positive infection compared to SGTF infection (aOR 0.91, 95%CI 0.68-1.22) (Supplementary table 1). The odds of severe disease was higher among individuals with a comorbidity (aOR 1.52, 95%CI 1.25-1.84) and among individuals aged 40-59 years (aOR 2.09, 95%CI 1.33-3.31) and ≥60 years (aOR 4.36, 95% CI 2.77-6.85), compared to individuals aged 19-24 years. Children aged 5-12 years (compared to 19-24 years), females, and individuals that had received ≥1 SARS-CoV-2 vaccine dose had a lower odds of severe disease.

Limitations of our study include restriction to samples tested with the TaqPath™ COVID-19 PCR assay, biasing data geographically, and that we used S gene positive infection as a proxy for BA.2 sub-lineage infection. Some misclassification could have occurred with other non-Omicron variants,

but these made up <2% of all detected viruses in December 2021 and January 2022. There could be a lag in hospitalisation and severe outcomes leading to underestimation of severe illness. To address this we only included hospitalised patients with known outcomes and censored cases to ensure there was at least 3 weeks of follow up. We only had vaccination information for hospitalised cases and this was based on self-report, and re-infection is likely under-ascertained due to limited testing.

We found a similar proportion of individuals were hospitalised and developed severe illness, given hospitalisation, for individuals infected with BA.1 compared to BA.2, during the Omicron-dominated fourth wave in South Africa. These data are reassuring, suggesting that while BA.2 may have a competitive advantage over BA.1 in some settings, the clinical profile of illness remains similar. South Africa may differ from other settings in having a high level of previous immunity following natural infection[5] and data evaluating BA.2 severity are needed from other settings.

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Table 1. Multivariable logistic regression analysis evaluating the association between S-gene positive infection, compared to S-gene target failure (SGTF) infection, and hospitalisation, South Africa, 1 December 2021 – 20 January 2022[a] (N=92,962)

		Hospital admission[b] n/N (%)	Adjusted odds ratio (95% CI)	P-value
SARS-CoV-2 sub-lineage		N=95,470		
	SGTF (BA.1 proxy)	2,965/87,194 (3.4)	Ref	Ref
	S-gene positive (BA.2 proxy)	295/8,276 (3.6)	0.96 (0.85-1.09)	0.536
Age group (years)		N=95,470		
	<5	226/1,681 (13.4)	7.49 (6.02-9.32)	**<0.001**
	5-12	98/4,426 (2.2)	1.16 (0.89-1.50)	0.274
	13-18	109/5,278 (2.1)	1.06 (0.83-1.37)	0.637
	19-24	146/7,127 (2.1)	Ref	Ref
	25-39	855/35,551 (2.4)	1.19 (0.99-1.42)	0.063
	40-59	847/30,953 (2.7)	1.39 (1.16-1.66)	**<0.001**
	≥60	979/10,454 (9.4)	4.97 (4.12-5.94)	**<0.001**
Sex		N=94,564		
	Male	1,364/42,017 (3.3)	Ref	Ref
	Female	1,884/52,547 (3.6)	1.14 (1.06-1.22)	**0.001**
Province		N=93,849		
	Eastern Cape	3/100 (3.0)	1.35 (0.42-4.35)	0.619
	Free State	78/2,126 (3.7)	1.35 (1.01-1.82)	**0.045**
	Gauteng	1,517/51,745 (2.9)	1.38 (1.14-1.66)	**0.001**
	KwaZulu-Natal	1,026/20,615 (5.0)	2.16 (1.78-2.62)	**<0.001**
	Limpopo	77/3,688 (2.1)	1.17 (0.88-1.57)	0.280
	Mpumalanga	179/4,559 (3.9)	2.13 (1.68-2.70)	**<0.001**
	North West	156/4,272 (3.7)	1.95 (1.53-2.49)	**<0.001**
	Northern Cape	33/1,203 (2.7)	0.97 (0.65-1.44)	0.861

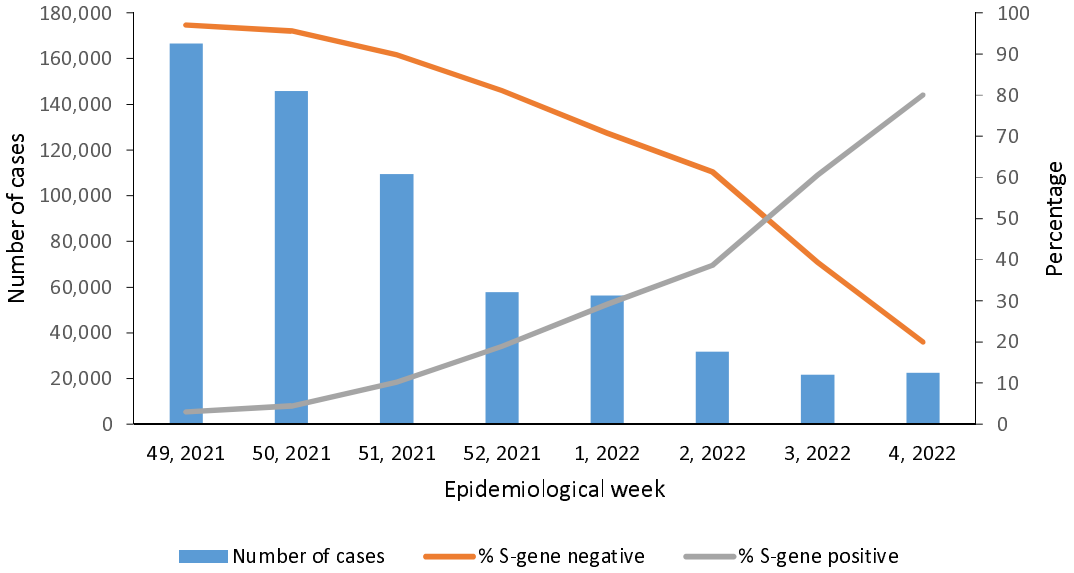
	Western Cape	122/5,541 (2.2)	Ref	Ref
Healthcare sector		N=95,470		
	Public	1,049/23,498 (4.5)	Ref	Ref
	Private	2,211/71,972 (3.1)	0.63 (0.58-0.68)	**<0.001**
Re-infection[c]		N=95,470		
	No	3,016/86,086 (3.5)	Ref	Ref
	Yes	244/9,384 (2.6)	0.99 (0.86-1.14)	0.857

[a] Cases followed-up for hospital admission until 10 February 2022

[b] Admission to hospital between 7 days prior to 21 days after diagnosis (specimen collection date)

[c] Re-infection was defined as an individual with at least one positive SARS-CoV-2 test >90 days prior to the current episode

Supplementary material



Supplementary Figure 1. Number of cases detected and percentage of S-gene positive and S-gene target failure (SGTF) infections among tests performed on the TaqPath assay by epidemiological week, DATCOV-Gen, 5 December 2021 – 29 January 2022

Supplementary table 1. Multivariable logistic regression analysis evaluating the association between S gene positive infection, compared to S-gene target failure (SGTF) infection, and severe disease among hospitalised individuals with known outcome, South Africa, 1 December 2021 – 20 January 2022[a] (N=2,984)

		Severe disease[a] n/N (%)	Adjusted odds ratio (95% CI)	P-value
SARS-CoV-2 sub-lineage		N=3,058		
	SGTF (BA.1 proxy)	929/2776 (33.5)	Ref	Ref
	S-gene positive (BA.2 proxy)	86/282 (30.5)	0.91 (0.68-1.22)	0.532
Age group (years)		N=3,058		
	<5	37/216 (17.1)	0.79 (0.45-1.39)	0.416
	5-12	8/92 (8.7)	0.38 (0.16-0.90)	**0.027**
	13-18	18/103 (17.5)	0.80 (0.41-1.57)	0.516
	19-24	28/139 (20.1)	Ref	Ref
	25-39	135/804 (16.8)	0.83 (0.52-1.33)	0.442
	40-59	284/790 (36.0)	2.09 (1.33-3.31)	**0.002**
	≥60	505/914 (55.3)	4.36 (2.77-6.85)	**<0.001**
Sex		N=3,046		
	Male	473/1,275 (37.1)	Ref	Ref
	Female	536/1,771 (30.3)	0.83 (0.70-0.98)	**0.031**
Province		N=2,994		
	Eastern Cape	1/3 (33.3)	2.21 (0.16-31.1)	0.556
	Free State	28/70 (40.0)	2.44 (1.19-5.02)	**0.015**
	Gauteng	509/1,384 (36.8)	2.79 (1.72-4.55)	**<0.001**
	KwaZulu-Natal	297/996 (29.8)	1.78 (1.08-2.94)	**0.025**
	Limpopo	10/76 (13.2)	0.81 (0.34-1.89)	0.623
	Mpumalanga	56/173 (32.4)	2.07 (1.13-3.77)	**0.018**
	North West	33/144 (22.9)	1.56 (0.83-2.95)	0.170

	Northern Cape	26/31 (83.9)	12.43 (4.10-37.63)	**<0.001**
	Western Cape	27/117 (23.1)	Ref	Ref
Co-morbidity[c]		N=3,058		
	Absent	636/2,244 (28.3)	Ref	Ref
	Present	379/814 (46.6)	1.52 (1.25-1.84)	**<0.001**
Healthcare sector		N=3,058		
	Public	377/965 (39.1)	Ref	Ref
	Private	638/2093 (30.5)	0.86 (0.70-1.07)	0.181
Days between diagnosis and admission		N=3,058		
	1-7 days before diagnosis	96/251 (38.3)	Ref	Ref
	0-6 days after diagnosis	803/2,496 (32.2)	0.82 (0.60-1.11)	0.196
	7-21 days after diagnosis	116/311 (37.3)	0.96 (0.65-1.41)	0.828
Re-infection[d]		N=3,058		
	No	963/2,831 (34.0)	Ref	Ref
	Yes	52/227 (22.9)	0.77 (0.54-1.11)	0.165
SARS-CoV-2 vaccination[e]		N=3,058		
	No	178/437 (40.7)	Ref	Ref
	Yes	43/169 (25.4)	0.52 (0.33-0.82)	**0.005**
	Unknown	794/2,452 (32.4)	0.75 (0.57-0.98)	**0.033**

[a] Cases followed-up for in-hospital outcome until 10 February 2022

[b] Severe disease defined as a hospitalised patient meeting at least one of the following criteria: admitted to ICU, received oxygen treatment, ventilated, received extracorporeal membrane oxygenation (ECMO), experienced acute respiratory distress syndrome (ARDS) and/or died

[c] Co-morbidity defined as ≥1 of the following conditions: hypertension, diabetes, chronic cardiac disease, chronic kidney disease, asthma, chronic obstructive pulmonary disease (COPD), malignancy, HIV, and active or past tuberculosis

[d] Re-infection was defined as an individual with at least one positive SARS-CoV-2 test >90 days prior to the current episode

[e] Vaccination defined as ≥1 dose of SARS-CoV-2 vaccine (Johnson & Johnson / Pfizer-BioNTech)

ETHICAL APPROVAL

Ethical approval was obtained from the Human Research Ethics Committee (Medical) of University of the Witwatersrand for the collection of COVID-19 case and test data as part of essential communicable disease surveillance (M210752), and for the DATCOV surveillance programme (M2010108).

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DATA SHARING STATEMENT

Data used in this manuscript are available upon reasonable request. Proposals should be directed to cherylc@nicd.ac.za.

AUTHOR CONTRIBUTIONS

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