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Clinical severity of COVID-19 patients admitted to hospitals in Gauteng, South Africa during the Omicron-dominant fourth wave

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Abstract:	Background : As Omicron became the dominant variant in South Africa, little is known about the severity of its clinical presentation. We describe the clinical severity of patients hospitalised with SARS-CoV-2 infection during the first four weeks of the Omicron-dominated fourth wave and compare this to the first four weeks of the Beta-dominated second and Delta-dominated third waves in Gauteng Province. Methods : Polymerase chain reaction and antigen positive SARS-CoV-2 case data were collated daily from laboratory reports. Data on hospital admissions were collected through an active surveillance programme established specifically for COVID-19. In addition to descriptive statistics, post-imputation random effect multivariable logistic regression models were used to compare disease severity in the three wave periods. Severe disease was defined as one or more of acute respiratory distress, supplemental oxygen, mechanical ventilation, high/intensive care or death. Results : There were 41,046, 33,423, and 133,551 SARS-CoV-2 cases in the second, third and fourth waves respectively. About 4.9% of cases were admitted to hospital during the fourth wave compared to 18.9% and 13.7% during the second and third waves (p<0.001). During the fourth wave, 28.8% of admissions were severe disease compared to 60.1% and 66.9% in the second and third waves (p<0.001). Admitted patients in the omicron-dominated fourth wave were 73% less likely to have severe disease than patients admitted during the delta-dominated third wave (adjusted odds ratio [aOR] 0.27, 95% confidence interval [CI] 0.25-0.31). Conclusion : The proportion of cases admitted was lower and those admitted were less severe during the first four weeks of the Omicron-dominated fourth wave in Gauteng province of South Africa. Since any combination of a less-virulent virus, co-morbidities, high immunity from prior infection(s) or vaccination may be important contributors to this clinical presentation, care should be taken in extrapolating this to

	other populations with different co-morbidity profiles, prevalence of prior infection and vaccination coverage.

Clinical severity of COVID-19 patients admitted to hospitals in Gauteng, South Africa during the Omicron-dominant fourth wave

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ABSTRACT

Background: As Omicron became the dominant variant in South Africa, little is known about the severity of its clinical presentation. We describe the clinical severity of patients hospitalised with SARS-CoV-2 infection during the first four weeks of the Omicron-dominated fourth wave and compare this to the first four weeks of the Beta-dominated second and Delta-dominated third waves in Gauteng Province.

Methods: Polymerase chain reaction and antigen positive SARS-CoV-2 case data were collated daily from laboratory reports. Data on hospital admissions were collected through an active surveillance programme established specifically for COVID-19. In addition to descriptive statistics, post-imputation random effect multivariable logistic regression models were used to compare disease severity in the three wave periods. Severe disease was defined as one or more of acute respiratory distress, supplemental oxygen, mechanical ventilation, high/intensive care or death.

Results: There were 41,046, 33,423, and 133,551 SARS-CoV-2 cases in the second, third and fourth waves respectively. About 4.9% of cases were admitted to hospital during the fourth wave compared to 18.9% and 13.7% during the second and third waves ($p<0.001$). During the fourth wave, 28.8% of admissions were severe disease compared to 60.1% and 66.9% in the second and third waves ($p<0.001$). Admitted patients in the omicron-dominated fourth wave were 73% less likely to have severe disease than patients admitted during the delta-dominated third wave (adjusted odds ratio [aOR] 0.27, 95% confidence interval [CI] 0.25-0.31).

Conclusion: The proportion of cases admitted was lower and those admitted were less severe during the first four weeks of the Omicron-dominated fourth wave in Gauteng province of South Africa. Since any combination of a less-virulent virus, co-morbidities, high immunity from prior infection(s) or vaccination may be important contributors to this clinical presentation, care should be taken in extrapolating this to other populations with different co-morbidity profiles, prevalence of prior infection and vaccination coverage.

INTRODUCTION

The fifth SARS-CoV-2 variant of concern, Omicron (B.1.1.529 lineage), was first publicly announced in South Africa on 25 November 2021 following its initial identification in the Gauteng Province (1). Within four weeks, Omicron had been reported by over 80 countries, and has driven a resurgence of SARS-CoV-2 cases in South Africa (2).

Genomic sequencing revealed that 81% (n=1,082) and 96% (n=356) of sequenced SARS-CoV-2 samples nationally were Omicron in November and December respectively (3). The proportion of ThermoFisher TaqPath COVID-19 reverse transcription polymerase chain reaction (rRT-PCR) positive tests with S-gene target failure, a marker of Omicron (4), was 3% (n=4), 97% (n=9,079) and 97% (n=14,810) in Gauteng in October, November and December respectively (5).

The predominant variants during Gauteng's first, second and third waves were the ancestral strain with a D614G mutation, Beta and Delta respectively. The mutations identified in Omicron suggest that it is likely to be highly transmissible with immune escape, but there are no data on whether it is associated with different clinical severity compared to previous variants (1). Clinical severity of COVID-19 is influenced by several factors, including age, sex, race, co-morbidities, previous SARS-CoV-2 infection and vaccination.

The prevalence of previous SARS-CoV-2 infection in Gauteng, was estimated to be 43% before the third wave (6) and 73% before the fourth wave (7). The South African COVID-19 vaccination programme began with healthcare workers from February 2021. It subsequently expanded to adults older than 60 years in May 2021 and then progressively over time to other age groups until adolescents 12-17 years were included in mid-October. As a result, vaccination coverage was low during the third wave but by 14 November 2021 before the fourth wave started, 31% of Gauteng's adult population were fully vaccinated with either BNT162b2 or Ad26.CoV2.S vaccine (8).

We aimed to describe the clinical severity of patients hospitalised with laboratory-confirmed SARS-CoV-2 infection during the first four weeks of the fourth wave and assess how this differed with comparable periods during the second and third waves in the Gauteng Province.

METHODS

We included data from Gauteng Province because Omicron was first identified in South Africa in this province and the rise in COVID-19 cases was experienced first in this province. Gauteng, which includes the cities of Johannesburg and Tshwane, is the most densely-populated province, with a mid-2020 population of 15,488,137 individuals (9).

Data on rRT-PCR and antigen positive SARS-CoV-2 cases were collated daily from laboratory reports (10) while data on COVID-19 hospital admissions were collected through DATCOV, an active surveillance programme established specifically for COVID-19 (11). Secondary data analysis for

Gauteng was conducted using the DATCOV national hospital surveillance database between 5 March 2020 and 11 December 2021. DATCOV surveillance collects data on all individuals with a positive SARS-CoV-2 rRT-PCR test or antigen test, with a confirmed duration of stay in hospital of one full day or longer, regardless of reason for admission. This included patients who had COVID-19 symptoms, were admitted for isolation, acquired nosocomial COVID-19 infection, or tested positive incidentally when admitted for other reasons. Some of the patients admitted in a wave may have been admitted in one or both of the previous two waves; these repeat admissions (more than 90 days after the first positive SARS-CoV-2 test) were included in the analysis.

The analysis was restricted to the first four weeks of each wave so that the equivalent periods of the second and third wave could be compared to the current period in the fourth wave. The early wave periods were defined from the week before the province crossed a weekly incidence risk of 30 cases per 100,000 persons until three weeks later (12)(13). The Omicron-dominated wave crossed the weekly incidence risk threshold in the last week of November 2021. Three weeks after the wave threshold was selected for this analysis because this is the maximum period for which data are currently available for the Omicron-dominated wave. The same four-week period for the Beta-dominated second wave and Delta-dominated third wave were selected for analysis. The start of each of these three wave periods selected also correlated with the majority of cases being due to the Beta, Delta and Omicron variants respectively (3).

- Wave 2: week 49 (2020)- week 52 (2020) (29 November-26 December 2020)
- Wave 3: week 18 (2021)- week 21 (2021) (2 May-29 May 2021)
- Wave 4: week 46 (2021)- week 49 (2021) (14 November-11 December 2021)

For hospitalisation and severity analyses, admissions were censored one week before data analysis as the median hospital stay for the combined three waves was 6 days (interquartile range 3;10), and this would allow for accumulation of hospital outcomes amongst those patients admitted during the study period. Analysis of severity was restricted to admissions that had already accumulated outcomes and all patients still in-hospital were excluded, because they were at risk of still developing severe outcomes or death. To assess whether exclusion of patients still in hospital at the time of analysis changed the results, the first 3,500 patients with outcome data from each of the three waves were analysed (Supplementary Table 1). Descriptive statistics were used to describe the trends in cases, admissions, severe disease and death over the equivalent four-week periods of the second, third and fourth waves.

Post-imputation random effect (on admission facility) multivariable logistic regression models were used to compare severe disease in the early second, third and fourth waves. To account for incomplete or missing data on selected variables, we used multivariate imputation by chained equation (MICE) and generated ten complete imputed datasets that were used for subsequent analyses. Variables analysed using MICE included race (6,026/17,255, 34.9% missing), and comorbidities (5,134/17,255, 29.8% missing). Complete variables included in the imputation process were age, sex, district, health sector (i.e. public or private), severity and in-hospital outcome (i.e. discharged alive or died). Severe disease

was defined as one or more of the following: development of acute respiratory distress syndrome, receipt of oxygen or invasive mechanical ventilation, treatment in high care or intensive care units (ICUs) or death. Age, sex, race, presence of a comorbidity (which included hypertension, diabetes, chronic cardiac disease, chronic kidney disease, asthma/chronic pulmonary disease, malignancy, HIV or tuberculosis), type of health sector (private or public) and health district were included in the model to assess the relationship between each wave period and severity in SARS-CoV-2 positive patients admitted to hospital.

Pairwise interactions were assessed by inclusion of product terms for all variables remaining in the final multivariable additive model. The statistical analysis was implemented using Stata 15 (Stata Corp®, College Station, Texas, USA). We followed STROBE guideline recommendations.

RESULTS

The province of Gauteng in South Africa experienced four distinct waves of SARS-CoV-2 infections, with approximately three-month periods of low transmission between each wave (Figure 1). The number of SARS-CoV-2 positive cases identified during each four-week period at the start of the wave was 41,046, 33,423, 133,551 in the Beta-, Delta- and Omicron-dominated waves respectively (Table 1). Unlike the pattern observed in the Beta and Delta waves, the rise in cases during the Omicron wave was not accompanied by a concomitant rise in hospital admissions (Figure 1). The percent of cases admitted was 18.9% (7,774/41,046) during the second wave and 13.7% (4,574/33,423) during the third wave compared to 4.9% (6,510/133,551) during the fourth wave (p=<0.001).

Of 6,510 SARS-CoV-2 positive patients admitted to hospital during the fourth wave, 2,072 (31.8%) were still in hospital as of 18 December 2021 and did not yet have a documented in-hospital outcome. In patients with known clinical outcomes, 60.1% (4,672/7,774) in the second wave and 66.8% (3,058/4,574) in the third wave compared to 28.8% (1,276/4,438) in the fourth wave met the criteria for severe disease (p=<0.001) (Table 2). The proportion of patients requiring supplemental oxygen was lower during the fourth wave (875/4,438, 19.7%) compared to the second wave (3,063/7,774, 39.4%) (p<0.001) or the third wave (2,231/4,574, 48.8%) (p<0.001) (Figure 2). Median hospital stay was 7 days (interquartile range [IQR]: 4-11), 8 days (IQR: 4-14) and 4 days (IQR: 2 -6 days) in the second, third and fourth waves respectively (p<0.001) (Table 2).

Children and adolescents constituted 3.9% (306/7,774), 3.5% (161/4,574) and 17.7% (1,151/6,510) of total admissions in the second, third and fourth waves. The percent of cases admitted among children and adolescents below 20 years was 7.1% (306/4,304), 3.8% (161/4,217) and 6.1% (1,151/18,817) across the three waves (Table 1). The proportion of hospitalised individuals aged <20 years who had severe disease was 22.5% (69/306), 23.0% (37/161) and 20.4% (172/844) in the three waves.

On multivariable analysis, patients admitted in the Omicron-dominated fourth wave were less likely than patients admitted in the Delta-dominated third wave, to have severe disease (adjusted odds ratio [aOR]

0.27, 95% confidence interval [CI] 0.25-0.31) (Table 3). Other factors associated with severe disease in this patient population were older age, male sex, and the presence of a comorbidity.

DISCUSSION

During the first four weeks of the Omicron-dominated fourth wave, the proportion of patients requiring hospital admission was substantially lower and those admitted had less severe illness, with fewer requiring oxygen, mechanical ventilation and intensive care compared to the first four weeks of the Beta- or Delta-dominated waves in Gauteng Province in South Africa. In-hospital case fatality ratios were over 4-fold lower during the Omicron-dominated wave compared to either the Beta- or Delta-dominated waves.

The number of adults aged >20 years admitted to hospital was lower in the fourth wave compared to both past waves leading to lower clinical burdens in health care services even in the midst of a much higher number of SARS-CoV-2 cases. Oxygen demand was lower and there was less pressure for ventilators and ICU beds during the fourth wave than in the second and third waves. Both the latter waves had approximately 3-fold higher number of patients with severe infection compared to the Omicron wave.

While admission rates during the fourth wave dropped substantially in those aged >20 years in whom vaccination coverage was higher, this was not observed in the largely unvaccinated <20 years age-group. In the <20 years group, the proportions of cases admitted to hospital was similar (7.1% vs 3.8% vs 6.1%) and the proportion with severe illness among admitted patients, was similar (22% vs 23.0% vs 20.4%) in the three waves, in contrast to the reductions in both admission rates and disease severity observed in the fourth wave in adults. Possible reasons for this could be that children have lower rates of prior infection (7) and/or vaccination (8).

An important consideration in the interpretation of these results is that they reflect only the early part of the waves prior to their peaks, when number of individuals hospitalised are low, patients with mild symptoms are more likely to be admitted as a precaution, and patients are diagnosed with SARS-CoV-2 infection incidentally when admitted for other reasons. While these considerations apply to the early part of all three waves, these results may not represent the entire Omicron-dominated wave's disease severity and may change when patient data for this entire wave are available. Additionally, 33% of the patients admitted during the Omicron-dominated wave were excluded from the analysis as they were still in hospital and severity of their infection has not been fully established yet. An alternative analysis of the first 3500 patients to reach an established outcome, produced similar results to the time-based analysis; indicating that the next 1,000 to 4,000 patients were similar to the first 3,500 patients in the other two waves. Obtaining the full clinical profile of Omicron infection will take several additional weeks when outcome data for the entire wave is available.

The reasons for the lower admission rates and less severe infections in admitted patients during the Omicron-dominated fourth wave are not known but are likely to be due to a less virulent virus, and high immunity from prior infection(s) or vaccination, especially the large numbers of vaccinated individuals who had prior infection and so have “hybrid immunity” (14). A tissue-based study showed that Omicron infects the cells of the bronchus faster but cells of the lung slower than Delta (15); which may at least partially account for the less severe infections observed in the Omicron-dominated wave.

Immunity stemming from prior infection has provided protection against symptomatic infection with previous variants (16) however preliminary data from South Africa (17) suggest that reinfections with Omicron are high. While prior infection may not prevent symptomatic breakthrough infection, it may generate T-cell responses that provide protection from severe disease (18), thereby contributing, at least partially to the observed high infection rate but low severity due to Omicron. The province of Gauteng experienced a particularly severe wave of Delta infection leading to a large increase in seroprevalence following the Delta-driven third wave. If prior infection with the Delta variant specifically provides some T-cell immunity that protects against severe disease from Omicron infection, this could be a contributor to the less severe Omicron infections observed in the Omicron-driven fourth wave.

While SARS-CoV-2 vaccine effectiveness in preventing symptomatic infection has been impacted by the emergence of variants (19), vaccination has reduced the risk of severe disease from past variants (20). Since vaccination coverage in Gauteng is higher in individuals aged above 60 years, it may have made an important contribution to the lower severity of Omicron infections, especially in the elderly. But vaccination cannot fully account for the markedly lower numbers of severe infections in 20-39 year-old individuals, as less than a third of this age group was vaccinated. One of the two vaccines being rolled out in South Africa is the Ad26.CoV2.S vaccine which generates lower antibody but better T-cell responses (21). The role of this specific vaccine in reducing disease severity but not clinical infections needs to be assessed.

A further consideration with regard to the impact of vaccines is that South Africa started vaccinations later than most high-income countries. As a result, a substantial number of vaccinated individuals had experienced prior infection. Vaccination in those with prior natural infection retains higher Omicron neutralisation than vaccination alone (22). The combination of natural immunity and vaccination may be a contributing factor to the observed lower severity of Omicron infections.

This study has some data limitations as well. Firstly, one of the limitations of this study is that disease severity relies on subjective clinical assessments and not laboratory parameters, although oxygen is usually initiated based on an objectively measured oxygen saturation. Secondly, the incompleteness of reporting in DATCOV and missing values in some patient data may under-estimate severity, but the completeness of reporting is unlikely to have changed over the three waves. Thirdly, early reporting on severe disease and case fatality rates underestimate severity as it may take a few weeks for hospitalisation outcomes to accumulate, particularly in older adults who may have longer admissions

and are more likely to die. We accounted for this by only including hospitalised patients with known outcomes and censoring admission to ensure at least one week follow up, as the median length of hospital stay was 6 days (IQR 3;10) across the three waves, which has allowed for the accumulation of most outcomes amongst patients admitted during the fourth wave study period. Fourthly, while the dataset did not have individual-level data on infecting lineage for cases included in this analysis, each of the three waves included in this study had a predominant variant that allows for wave period to be used as a proxy for dominant variant. During the four weeks of the fourth wave included in this study, gene sequencing as well as S-gene target failure showed that over 90% of circulating viruses were omicron. Fifthly, DATCOV contains incomplete data on prior SARS-CoV-2 infection and vaccination status, which severely limits exploration of their potential roles in lower disease severity observed. In South Africa infection and re-infection are substantially under-ascertained due to the high proportion of asymptomatic infections. Data on COVID-19 hospital admissions are collected at health service level by clinicians and nurses and contains limited data on self-reported vaccination status; vaccination data is collected in a different system and linkage of the two data systems is still underway. This has meant that the role of vaccination could not readily be studied in relation to clinical severity of COVID-19. This limitation has highlighted the need for the creators of the different surveillance datasets to ensure compatibility and potential for integration.

CONCLUSION

Early surveillance data indicate that Omicron, which is the predominant variant during South Africa's fourth wave, is associated with lower hospital admission rates and with lower severity and lower fatality among hospitalised patients. The role of prior immunity from natural infection, vaccination and/or lower virulence needs to be investigated as all these factors may be contributing to some extent. These results may not be directly applicable to other countries and settings. It remains to be seen whether other countries experience similar lower risk of severe disease, considering the differences in population structure, co-morbidity prevalence, prevalence of prior infection and vaccination coverage. Further, in some countries, Omicron-dominated waves began during a period of high Delta transmission whereas the Omicron-dominated fourth wave in South Africa began when Delta infection rates were very low. Overall, a well-developed surveillance system for variant identification and hospital admissions is essential as part of pandemic preparedness to rapidly investigate the impact of new SARS-CoV-2 variants and viruses causing future pandemics.

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CONTRIBUTORSHIP

WJ, SSAK, CM contributed to literature search. WJ, LB, CC, LO, CM contributed to study design and refining methods of analysis. CM, WJ, SSAK and RW contributed to data analysis, and creation of tables and figures. WJ, SSAK, CC and CM contributed to data interpretation and initial draft. WJ and SSAK drafted the initial manuscript and all other co-authors contributed scientific inputs equally towards the interpretation of the findings and the final draft of the manuscript. WJ, CM, RW and LO have verified the underlying data.

DATA SHARING AGREEMENT

The dataset analysed for the manuscript is available upon reasonable request. The data dictionary is available at request to the corresponding author: waasilaj@nicd.ac.za

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

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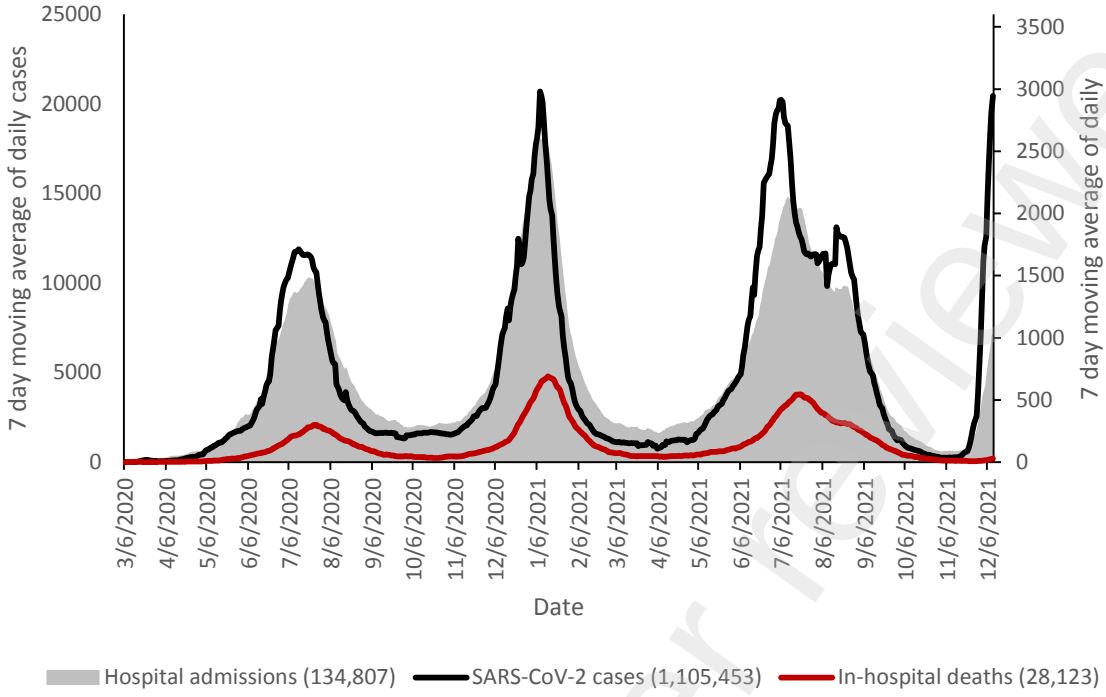

Figure 1: 7 day moving average of SARS-CoV-2 cases, COVID-19 admissions and in-hospital deaths in Gauteng Province of South Africa, 5 March 2020-11 December 2021.

Table 1: Summary of SARS-CoV-2 cases, COVID-19 admissions and in-hospital deaths in the Beta- (29 Nov-26 Dec 2020), Delta- (2 May-29 May 2021) and Omicron-dominated waves (14 Nov-11 Dec 2021), Gauteng Province, South Africa

Variant wave	Number of SARS-CoV-2 positive cases	Incidence of SARS-CoV-2 positive cases per 100,000 persons	Percent (Number) of cases admitted to hospital	Percent (Number) of admitted cases with an outcome who died in hospital (n)
All ages (population 15,488,137; fully vaccinated 30.9%*)				
Beta	41046	265.0	18.9 (7774)	24.3 (1892)
Delta	33423	215.8	13.7 (4574)	24.2 (1107)
Omicron	133551	862.3	4.9 (6510)	5.8 (258)
Age <20 years (population 4,710,102, fully vaccinated 5.8%*)				
Beta	4304	91.4	7.1 (306)	2.0 (6)
Delta	4217	89.5	3.8 (161)	1.9 (3)
Omicron	18817	399.5	6.1 (1151)	1.3 (11)
Age 20-39 years (population 6,140,703; fully vaccinated 31.7%*)				
Beta	18108	294.9	9.4 (1697)	8.4 (142)
Delta	10801	175.9	6.6 (714)	9.2 (66)
Omicron	67282	1095.7	3.9 (2624)	2.3 (43)
Age 40-59 years (population 3,327,121; fully vaccinated 54.3%*)				
Beta	14001	420.8	22.8 (3188)	20.4 (651)
Delta	13110	394.0	12.9 (1685)	16.6 (279)
Omicron	38266	1150.1	3.8 (1441)	7.9 (78)
Age >60 years (population 1,310,211; fully vaccinated 58.4%*)				
Beta	4633	353.6	55.8 (2583)	42.3 (1093)
Delta	5295	404.1	38.0 (2014)	37.7 (759)
Omicron	9186	701.1	14.1 (1294)	16.8 (126)

*Vaccination coverage data for Omicron wave is from 14 November 2021 (National Department of Health. Latest Vaccine Statistics. https://sacoronavirus.co.za/latest-vaccine-statistics/)

Table 2: Indicators of disease severity among SARS-CoV-2 positive cases admitted in the Beta- (29 Nov-26 Dec 2020), Delta- (2 May-29 May 2021) and Omicron-dominated waves (14 Nov-11 Dec 2021), Gauteng Province, South Africa

Variant wave	Number of cases admitted to hospital with known outcome	Median length of stay in days (IQR)	Percent (Number) of admitted cases who received supplemental oxygen (n)	Percent (Number) of admitted cases who were treated in ICU (n)	Percent (Number) of admitted cases who had severe disease (n)
All ages					
Beta	7774	7 (4;11)	39.4 (3063)	20.0 (1552)	60.1 (4672)
Delta	4574	8 (4;14)	48.8 (2231)	26.2 (1198)	66.9 (3058)
Omicron	4438	4 (2;6)	19.7 (875)	6.9 (308)	28.8 (1276)
Age <20 years					
Beta	306	4 (2;8)	14.7 (45)	3.9 (12)	22.5 (69)
Delta	161	3 (2;8)	15.5 (25)	9.9 (16)	23.0 (37)
Omicron	844	3 (2;5)	13.0 (110)	4.3 (36)	20.4 (172)
Age 20-39 years					
Beta	1697	5 (3;9)	31.3 (532)	11.5 (195)	42.6 (723)
Delta	714	6 (3;11)	35.4 (253)	14.0 (100)	46.6 (333)
Omicron	1862	3 (2;6)	13.0 (242)	3.6 (67)	19.1 (355)
Age 40-59 years					
Beta	3188	7 (4;11)	42.6 (1358)	21.6 (689)	61.9 (1972)
Delta	1685	8 (5;13)	51.1 (861)	27.2 (459)	67.2 (1132)
Omicron	983	4 (2;7)	22.8 (224)	9.5 (93)	34.2 (336)
Age ≥60 years					
Beta	2583	8 (4;13)	43.7 (1128)	25.4 (656)	73.9 (1908)
Delta	2014	9 (5;16)	54.2 (1092)	30.9 (623)	77.3 (1556)
Omicron	749	5 (3;9)	39.9 (299)	15.0 (112)	55.1 (413)

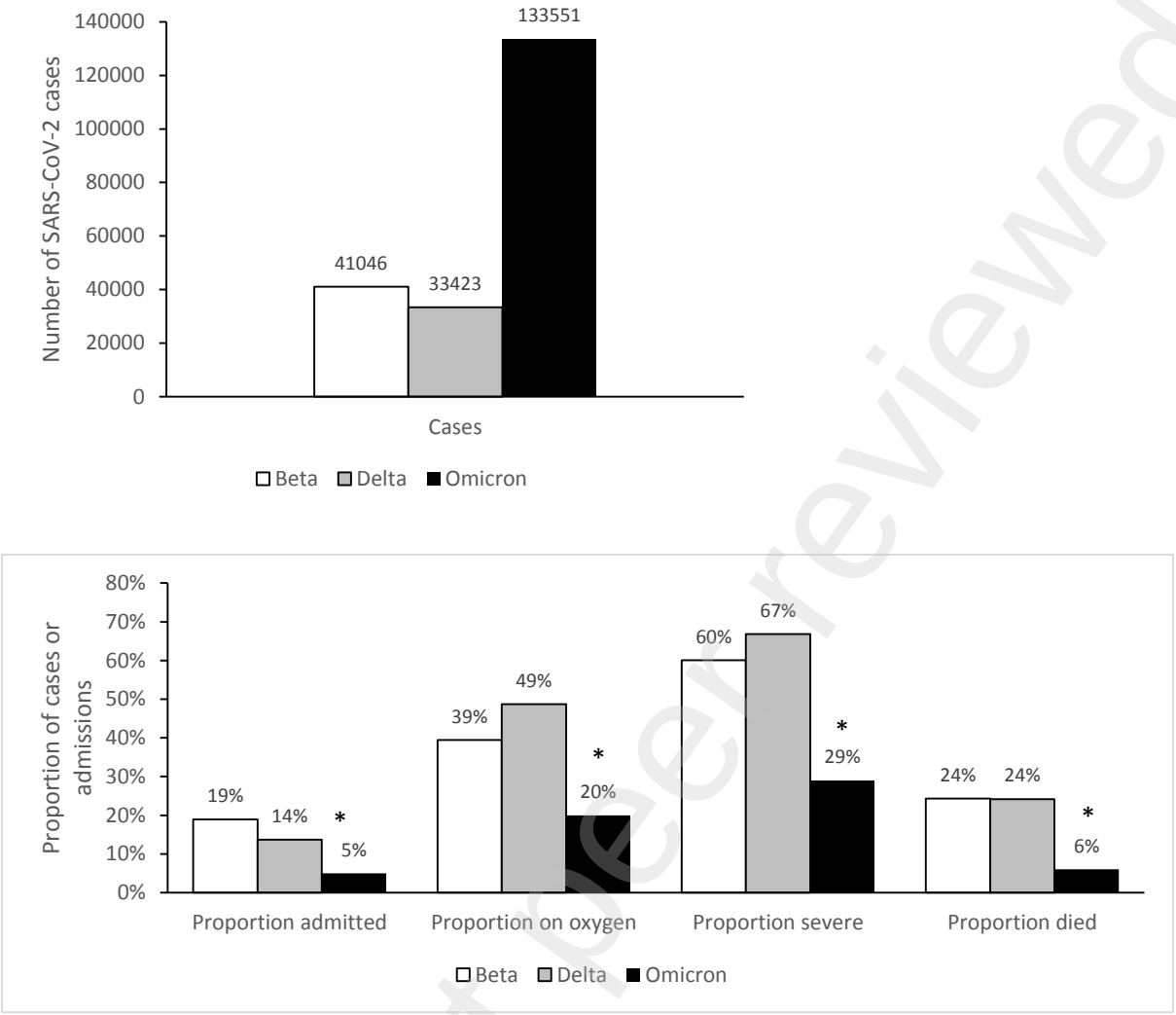

Figure 2a: Number of SARS-CoV-2 cases, and **Figure 2b**: Percent of cases admitted, percent of admissions who received supplementary oxygen, with severe disease, and in-hospital deaths, for individuals of all ages, in the Beta- (29 Nov-26 Dec 2020), Delta- (2 May-29 May 2021) and Omicron-dominated waves (14 Nov-11 Dec 2021), Gauteng Province, South Africa.

* p<0.001 using Pearson chi2 or Mann-Whitney test comparing fourth wave to the second and third waves respectively

Table 3. Factors associated with severe disease among SARS-CoV-2 positive hospitalised patients in the Beta- (29 Nov-26 Dec 2020), Delta- (2 May-29 May 2021) and Omicron-dominated waves (14 Nov-11 Dec 2021), Gauteng Province, South Africa. (univariate and multivariable analysis implemented on the imputed dataset) (N=16,786)

Characteristic	Proportion severe % (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p value
Age group (years)				
<20	21.2 (19.0-23.4)	Reference	Reference	
20-39	33.0 (31.6-34.4)	2.20 (1.87-2.59)	1.69 (1.42-2.00)	<0.001
40-59	58.7 (57.5-60.0)	6.40 (5.46-7.50)	3.40 (2.87-4.02)	<0.001
60+	72.5 (71.3-73.7)	11.87 (10.08-13.98)	6.04 (5.06-7.20)	<0.001
Sex				
Female	49.8 (48.8-50.8)	Reference	Reference	
Male	58.4 (57.3-59.5)	1.36 (1.27-1.45)	1.27 (1.18-1.36)	<0.001
Race				
White	66.0 (64.0-67.9)	Reference	Reference	
Mixed	56.9 (51.8-62.0)	1.94 (1.72-2.18)	0.93 (0.72-1.21)	0.59
Black	48.9 (48.0-49.8)	1.33 (1.06-1.65)	0.95 (0.83-1.09)	0.47
Indian	67.0 (63.1-71.0)	2.25 (1.86-2.71)	1.24 (0.99-1.55)	0.065
Other	55.7 (45.3-66.1)	1.13 (0.70-1.82)	0.93 (0.54-1.58)	0.78
Comorbid condition				
No co-morbidity	46.1 (45.0-47.1)	Reference	Reference	
Co-morbid condition	65.3 (64.1-66.5)	2.60 (2.36-2.86)	1.63 (1.46-1.82)	<0.001
Health sector				
Private sector	54.6 (53.6-55.5)	Reference	Reference	
Public sector	52.3 (51.1-53.5)	0.98 (0.59-1.63)	1.06 (0.64-1.76)	0.81
District				
City of Johannesburg Metro	52.9 (51.6-54.2)	Reference	Reference	
City of Tshwane Metro	53.2 (51.8-54.5)	1.13 (0.63-2.05)	1.29 (072-2.30)	0.40
Ekurhuleni Metro	54.4 (52.7-56.2)	1.32 (0.69-2.52)	1.32 (0.70-2.49)	0.38
Sedibeng	61.9 (58.9-64.9)	1.77 (0.69-4.55)	1.20 (0.48-3.00)	0.70
West Rand	51.1 (48.7-53.6)	1.09 (0.43-2.77)	0.98 (0.39-2.43)	0.96
Wave period				
Early wave 3	66.9 (65.5-68.2)	Reference	Reference	
Early wave 2	60.1 (59.0-61.2)	0.86 (0.79-0.94)	0.95 (0.87-1.04)	0.27
Early wave 4	28.8 (27.4-30.1)	0.18 (0.16-0.19)	0.27 (0.25-0.31)	<0.001

OR=Odds Ratio; CI=Confidence Interval

SUPPLEMENTARY MATERIAL

Supplementary table 1: SARS-CoV-2 cases, COVID-19 admissions and in-hospital deaths and indicators of severity among the first 3,500 SARS-CoV-2 positive admissions with outcome data in the Beta- (29 Nov-21 Dec 2020), Delta- (2 May-24 May 2021) and Omicron-dominated waves (14 Nov-9 Dec 2021), Gauteng Province, South Africa.

Indicator	Variant wave		
	Beta	Delta	Omicron
Number of hospital admissions with an available outcome status	3500	3500	3500
Proportion (%) of admitted cases who received supplemental oxygen in hospital (n)	34.9 (1223)	48.5 (1697)	17.5 (611)
Proportion (%) of admitted cases who were treated in ICU in hospital (n)	20.0 (700)	26.7 (934)	6.3 (220)
Proportion (%) of admitted cases who had severe disease in hospital (n)	55.2 (1933)	67.0 (2346)	26.6 (932)
Proportion (%) of admitted cases with an outcome who died in hospital (n)	20.5 (719)	24.3 (852)	5.0 (174)
Median length of stay (days).	7 (4;11)	8 (4;14)	3 (2;5)