

South African Population Immunity and Severe Covid-19 with Omicron Variant

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ABSTRACT

Background

We conducted a seroepidemiological survey from October 22 to December 9, 2021, in Gauteng Province, South Africa, to determine SARS-CoV-2 immunoglobulin G (IgG) seroprevalence primarily prior to the fourth wave of coronavirus disease 2019 (Covid-19), in which the B.1.1.529 (Omicron) variant is dominant. We evaluated epidemiological trends in case rates and rates of severe disease through to December 15, 2021, in Gauteng.

Methods

We contacted households from a previous seroepidemiological survey conducted from November 2020 to January 2021, plus an additional 10% of households using the same sampling framework. Dry blood spot samples were tested for anti-spike and anti-nucleocapsid protein IgG using quantitative assays on the Luminex platform. Daily case and death data, weekly excess deaths, and weekly hospital admissions were plotted over time.

Results

Samples were obtained from 7010 individuals, of whom 1319 (18.8%) had received a Covid-19 vaccine. Overall seroprevalence ranged from 56.2% (95% confidence interval [CI], 52.6 to 59.7) in children aged <12 years to 79.7% (95% CI, 77.6 to 81.5) in individuals aged >50 years. Seropositivity was 6.22-fold more likely in vaccinated (93.1%) vs unvaccinated (68.4%) individuals. Epidemiological data showed SARS-CoV-2 infection rates increased more rapidly than in previous waves but have now plateaued. Rates of hospitalizations and excess deaths did not increase proportionately, remaining relatively low.

Conclusions

We demonstrate widespread underlying SARS-CoV-2 seropositivity in Gauteng Province prior to the current Omicron-dominant wave, with epidemiological data showing an

uncoupling of hospitalization and death rates from infection rate during Omicron
circulation.

BACKGROUND

The B.1.1.529 (Omicron) variant of severe acute respiratory virus syndrome coronavirus 2 (SARS-CoV-2) was first reported on November 25, 2021, in Gauteng Province, South Africa.¹ The World Health Organization designated Omicron a variant of concern due to its predicted greater transmissibility and its potential to evade vaccine- and natural infection-induced immunity.² The Omicron variant contains mutations that indicate it could be more infectious (R203K, G204R mutations affecting the nucleocapsid protein), more transmissible (H655Y, N679K, P681H mutations affecting the spike protein), and possibly better able to evade innate immunity (Δ 105-107 mutation affecting nonstructural proteins) and antibodies (multiple mutations affecting the spike protein receptor binding domain [RBD] and N-terminal domain) compared with the wild-type (WT) variant.^{3,4} In addition to at least 32 mutations affecting the spike protein,⁵ the Omicron variant harbors three mutations affecting the membrane protein and six involving the nucleocapsid protein, compared with only seven spike and one nucleocapsid-protein mutation in the antibody-evasive B.1.351 (Beta) variant.⁶

The Omicron variant has out-competed the B.1.617.2 (Delta) variant in Gauteng Province and is now responsible for approximately 95% of new cases sequenced.⁷ This fourth wave of Covid-19 is occurring in the context of the rollout of Covid-19 vaccines, which began on May 17, 2021. We previously conducted a population-wide seroepidemiological survey in Gauteng that was completed on January 22, 2021, nine weeks into the second wave of Covid-19 in South Africa, a wave dominated by the Beta variant.⁸ We found that 19.1% of the population were anti-RBD IgG seropositive, a value that ranged from 5% to 43% across provincial sub-districts.⁸ Since that time, South Africa has experienced a third wave of Covid-

19 from April 7 to November 1 that was largely due to the Delta variant, which out-competed the Beta variant.⁹

Herein, we report a follow-up seroepidemiological survey in Gauteng Province that was completed on December 9, 2021, and thus provides seroprevalence data largely from prior to the fourth wave. Furthermore, we report epidemiological trends for rates of Covid-19 cases, hospitalizations, recorded deaths, and excess mortality for Gauteng Province from the start of the pandemic through to December 15, 2021.

METHODS

Study setting and data collection

Gauteng Province is demarcated into five health districts comprising 26 sub-districts.¹⁰ It constitutes 1.5% of South Africa's landmass but contains 26% (15.9/59.6 million) of its population.¹⁰ The overall population density (people per square kilometer) in Gauteng Province is 737, ranging from 3400 in the Johannesburg district, where 36.9% of the population live, to 200 in West Rand, in which 6.2% of the population live (Table S1 in the Supplementary Appendix).

This survey included the same households sampled during our previous survey, which was undertaken from November 4, 2020, to January 22, 2021,⁸ nine weeks after the onset of the second wave of Covid-19 in Gauteng Province, which was dominated by the Beta variant. Details of the previous survey, including the sampling framework used, have been published.⁸ In the survey reported here, which was conducted from October 22 to December 9, 2021, an additional 10% of households were sampled in the same clusters to

accommodate for possible non-participation, out-migration, and death of individuals since the previous survey. The survey was powered to evaluate seropositivity to SARS-CoV2 at the district and sub-district level. Demographic and epidemiologic data were collected using an electronic questionnaire.⁸

Serology analysis

Dried blood spot samples were collected from participating individuals and tested for anti-spike and anti-nucleocapsid protein IgG (see Supplementary Methods section of the Supplementary Appendix). Anti-nucleocapsid IgG was included to identify individuals who were seropositive from natural infection rather than due to vaccination (i.e. only anti-spike IgG seropositivity). Details of the serology assay have been published and are summarized in the Supplementary Methods section of the Supplementary Appendix.^{11,12}

Covid-19 data sources

Daily case and death data were sourced from the South African national coronavirus database produced by the National Department of Health.¹³ Weekly excess death data were sourced from the South African Medical Research Council.¹⁴ Weekly hospital admissions data were sourced from the National Institute for Communicable Disease DATCOV database (latest report from December 11, 2021).¹⁵ We analyzed the epidemiological data for Covid-19 cases, hospitalization, recorded deaths, and excess mortality rates for Gauteng Province and its five health districts.

Statistical analyses

Sample size justification, random household repeat sampling methods of households in our previous survey, and details of the multivariate analysis identifying associations with seropositivity have been published previously and are summarized in the Supplementary Methods section of the Supplementary Appendix.⁸ For the calculation of case, hospitalization, and death rates, data were smoothed using a 7-day moving average in STATA version 16.1; weekly rates are unsmoothed.

Survey Ethics

The Human Research Ethics Committee at the University of the Witwatersrand granted a waiver for ethics approval of the survey, which was being done at the behest of Gauteng Department of Health as part of public health surveillance. Nevertheless, informed consent was obtained from all individuals, who were able to decline participation.

RESULTS

Participants

We obtained adequate samples for serostatus evaluation from 7010 of 7498 individuals, in 3047 households (Figure 1); 83% of samples had been obtained by November 25, when the Omicron variant was first reported (Figure S1 in the Supplementary Appendix). Demographic and household characteristics, prevalence of known underlying medical conditions and self-reported HIV status, and vaccination rates are shown in Table 1. Vaccination rates in Gauteng Province by district, age, and vaccine are summarized in Table S2 in the Supplementary Appendix. As of November 25, 2021, of the total population of 12,191,569 people aged more than 12 years eligible for vaccination, 4,386,646 (36.0%) had received at

least one dose of BNT162b2 or Ad26.CoV2.S, and 2,452,017 (20.1%) had received two doses.

Of those aged more than 50 years, 1,074,303/2,416,045 (44.5%) had received two doses of BNT162b2 (Table S2).

Seroprevalance

In unvaccinated individuals, the overall rate of anti-spike or anti-nucleocapsid IgG seropositivity was 68.4% (95% confidence interval [CI], 67.2 to 69.6) (Table 1), whereas the rate of anti-nucleocapsid IgG seropositivity was 39.7% (2259/5691; 95% CI, 38.4 to 41.0), indicating a lack of sensitivity of anti-nucleocapsid IgG for detecting previous infection. We thus focused on the overall rate of anti-spike or anti-nucleocapsid IgG seropositivity.

The overall seroprevalence rate was 73.1% (95% CI, 72.0 to 74.1). The rate was heterogeneous across provincial districts (Figure 2), ranging from 66.7% (95% CI, 54.2 to 69.0) in Tshwane, where the Omicron variant was first identified, to 76.2% (95% CI, 74.5 to 77.8) in Johannesburg (Table 1). Compared with Johannesburg, seroprevalence was lower in Sedibeng and Tshwane (Table 1). The rate was also heterogeneous at the sub-district level, with seropositivity rates ranging from 72.7% to 85.8% in Johannesburg and from 58.9% to 77.4% in City of Tshwane district (Table S3).

Females (76.9%) were 1.43-fold (adjusted odds ratio; 95% CI, 1.27 to 1.62) more likely to be seropositive than males (67.9%) (Table 1). Seropositivity rate varied by age-group, being lowest in children aged less than 12 years (56.2%) and highest in individuals aged more than 50 years (79.7%). Children aged 12–18 years (73.8%) were 2.2-fold (unadjusted odds ratio; 95% CI, 1.75 to 2.76) more likely to be seropositive than those aged less than 12 years.

Covid-19-vaccinated individuals had 6.22 (unadjusted odds ratio; 95% CI, 4.99 to 7.75) greater odds of being seropositive (93.1%) than unvaccinated people (68.4%), with consistently high seropositivity rates across age groups and higher odds of seropositivity in vaccinated compared with unvaccinated individuals aged 18–50 years (Table 1).

Individuals who had previously tested positive for SARS-CoV-2 had 1.94-fold higher odds (adjusted ratio; 95% CI, 1.23 to 3.08) of being seropositive (88.2%) than those who had never been tested (71.7%). Seropositivity rate in self-reported HIV-positive individuals (72.0%) was 0.73-fold (adjusted odds ratio; 95% CI, 0.59 to 0.90) lower than in HIV-negative individuals (73.2%). Compared with participants living in a stand-alone dwelling (74.2%), participants resident in high-rise dwellings had 1.33-fold (adjusted odds ratio; 95% CI, 1.03 to 1.71) higher odds of seropositivity (77.8%), whereas living in an informal settlement was associated with 0.78-fold lower odds (adjusted ratio; 95% CI, 0.67 to 0.90) of seropositivity (66.3%). Daily smoking (66.5%) was associated with 0.69-fold lower odds (adjusted ratio; 95% CI, 0.59 to 0.80) of seropositivity compared with not smoking (77.6%) (Table 1).

Covid-19 rates

Daily case rates, weekly hospitalization rates, and weekly excess death rates per 100,000 population, and daily recorded death rates per 1,000,000 population in Gauteng Province are shown in Figure 3. In the current Omicron-dominant wave, the daily case rate increased at a faster rate than prior waves, with 164,911 cases in the first 31 days, compared with 38,577 in the first 31 days of the Delta-dominant third wave (Table 2). The rate has now peaked at a lower maximum level than in the third wave (Figure 3). Time from onset to peak of the current wave was 1 month, compared with 2 months in the third wave. In comparison

with the third wave, weekly hospitalization rates at corresponding daily case rates are considerably lower, with 3432 versus 10,088 hospitalizations in the first 31 days, as are weekly excess deaths (total 569 vs 2650 in the first 31 days), and daily reported death rates (total 194 vs 668 in the first 31 days) (Figure 3, Table 2). Although rates differ, similar trends were observed across all districts (Figure S2). Although there is a lag in excess death reporting (December 11, 2021), the current rate of 1 per 100,000 is lower than 25 per 100,000 at the peak of the third wave (Figure 3).

DISCUSSION

The current resurgence of Covid-19 in Gauteng Province due to the Omicron variant comes at a time when Covid-19 vaccine coverage is 36.0% in people aged more than 12 years, with only 20.1% having received at least two doses of a Covid-19 vaccine as part of the national vaccine roll-out program. Nevertheless, our survey shows widespread underlying SARS-CoV-2 seropositivity across the province (73.1%), including up to 85.8% in some sub-districts, prior to the onset of the current Omicron-dominant wave. This high rate of seropositivity has been induced by prior SARS-CoV-2 infection, as evidenced by the 68.4% seropositivity rate in Covid-19-unvaccinated individuals.

In this context, we have observed a dramatic uncoupling of hospitalization and death rates from infection rate compared with previous waves. We have seen a high Covid-19 case rate due to the Omicron variant despite the high seropositivity rate for humoral immune responses, consistent with the Omicron variant being antibody-evasive. However, the peak hospitalization rate in the current wave is 29% of the peak in the Delta-dominant third wave (13 and 44 per 100,000, respectively), while both reported daily and weekly excess deaths

are at levels typical of troughs between waves (Figure 3). The virulence of the Omicron variant relative to other variants remains to be determined, and it is not epidemiologically possible to draw conclusions based on our data due to the differing prevalence of immunity compared with what existed in the past.

The biological basis for the uncoupling of case rates and rates of severe disease with the Omicron-dominant compared with the previous Delta-dominant wave is possibly the extensive cell-mediated immunity in the population induced by previous natural infection and vaccination, for which coverage of at least one dose is 61.2% (1,479,288/2,416,045) in adults aged more than 50 years (who accounted for 81% [22,269/27,500] of all deaths in Gauteng Province through to the end of the third wave¹⁶). Although we did not evaluate cell-mediated immunity, other studies have reported that natural infection induces a diverse polyepitopic cell-mediated immune response targeted against the spike protein, nucleocapsid protein, and membrane protein.¹⁷ Consequently, cell-mediated immunity is likely more durable than antibody-mediated immunity in the context of small mutations, particularly those mainly affecting the spike protein, as in the Omicron variant. Furthermore, natural infection induces robust memory T-cell responses, including long-lived cytotoxic (CD8⁺) T-cells, which have a half-life of 125–255 days.¹⁸ We believe that the evolution of cell-mediated immunity from prior natural infection and vaccination is resulting in the uncoupling of the high case rates seen with the Omicron variant and the rates of severe disease. This is despite the Omicron variant evading neutralizing activity induced by spike-protein-based vaccines and by prior infections with other variants not harboring the same full set of putatively antibody-evasive mutations.

Reports indicate that the Omicron variant is more evasive to neutralizing antibody activity than even the Beta variant.^{6,19,20} Relative to vaccine-induced neutralizing antibody activity against WT virus, neutralizing activity after two doses of BNT162b2 or AZD1222 (ChAdOx1 nCoV-19) is reduced substantially.^{21,22} Nevertheless, the majority of individuals with hybrid immunity from natural infection and BNT162b2 or AZD1222 vaccination have measurable neutralizing activity against the Omicron variant, albeit lower than against the WT virus.¹⁹ In this context, the high rate of breakthrough cases and reinfections with the Omicron variant is to be expected in South Africa, where the majority of individuals have developed immunity from natural infection, which induces lower-magnitude anti-spike neutralizing and binding antibody responses compared with vaccination.²⁰ Furthermore, South Africa is currently only providing a single dose of Ad26.COV2.S as part of its vaccine rollout, which induces lower neutralizing and blocking antibody titers than two doses of the BNT162b2,²⁰ and third doses of BNT162b2 are yet to be introduced in South Africa.

This clinical evidence of the antibody-evasiveness of the Omicron variant is corroborated by early studies reporting limited vaccine efficacy (VE) against Omicron at 25 weeks after two doses of AZD1222 or BNT162b2.²³ However, VE increased substantially at 2 weeks after a booster dose of BNT162b2,²³ which results in much higher neutralizing antibody titers than after two doses of vaccine²⁴ and thus may partly mitigate the relative antibody-evasiveness of the Omicron variant. Similarly, in South Africa, vaccine effectiveness against symptomatic Covid-19 due to the Omicron variant was 30%; however, protection against hospitalization was 70%, compared to 90% observed against the Delta variant.²⁵ These data, together with the very limited neutralizing antibody activity against the Omicron variant following two doses of AZD1222 or BNT162b2, further corroborate that protection against severe Covid-19

is likely mediated by much lower neutralizing antibody titres²⁰ or primarily through cell-mediated immunity.

Analogous to the emerging experience with the Omicron variant is the antibody-evasiveness of the Beta variant in recipients of AZD1222, which showed no VE against mild-to-moderate Covid-19 due to the Beta variant.²⁶ However, effectiveness of 80% against hospitalization or death due to the Beta or Gamma variants has been reported from Canada.²⁷ While AZD1222 induced nominal neutralizing antibody activity against the Beta variant, only 11 of the 87 spike-protein epitopes targeted by T-cell immune responses induced by AZD1222 were affected by mutations in the Beta variant.²⁶ The dissociation between the lack of AZD1222-induced neutralizing antibody activity and protection against severe lower respiratory tract disease was also observed in a challenge study with AZD122 against the Beta variant in a Syrian golden hamster model.²⁸

The greater transmissibility of the Omicron variant is corroborated by the rapid rise of reported Covid-19 cases in Gauteng Province during the course of the current wave. Indeed, the rate of increase in cases exceeds any of the previous three waves, indicating that the Omicron variant is more transmissible than even the Delta variant, which has an estimated reproductive rate (Ro) of 5-6.²⁹

Limitations of our study include the use of publically available data on Covid-19 morbidity and mortality that was collated in surveillance systems and could have changed over time, which could affect comparisons across the four waves. DATCOV surveillance does not distinguish between SARS-CoV-2 cases hospitalized for Covid-19 and those admitted for

other illness who coincidentally test positive for SARS-CoV-2 on routine screening.

Nevertheless, these systems are unlikely to have changed since the Delta-dominant third wave. Another limitation is that the current wave is only in its fourth week at data cut-off, although the 7-day rolling average of case rate has plateaued and is on a downward trend. Also, our contention that cell-mediated immunity primarily due to natural infection, with or without Covid-19 vaccination, is resulting in the uncoupling of case rates and severe disease remains to be investigated. In particular, the extent to which the polyepitopic T-cell responses induced by vaccination against the spike-protein and the even more diverse polyepitopic T-cell response stimulated by natural infection, with or without vaccination, warrant investigation.

As there may be a 1-2 week lag between the surge in SARS-CoV-2 infections and severe Covid-19 cases, monitoring is ongoing to determine whether the uncoupling of case rate and rate of severe illness remains during the current Omicron-dominant wave. If so, we believe it may herald a turning point in the Covid-19 pandemic, if the primary goal is protection against severe disease and death rather than trying to prevent infections. The 70% effectiveness seen with BNT162b2 against severe disease in South Africa²⁵ might well be due to the hybrid cell-mediated immunity induced by vaccination and natural infection. Whether the same protection against severe Covid-19 due to the Omicron variant will be seen in countries in which immunity is mainly from vaccination remains to be determined.

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DATA SHARING

Data are available at www.wits-vida.org; requests for data sharing should be directed to Professor Shabir A. Madhi, email: Shabir.Madhi@wits.ac.za

DISCLOSURES

Dr. Madhi reports grants from the Bill & Melinda Gates Foundation during the conduct of the study, grants and personal fees from the Bill & Melinda Gates Foundation, grants from the South African Medical Research Council, grants from Novavax, grants from Pfizer, grants from Minervax, and grants from the European & Developing Countries Clinical Trials Partnership, outside the submitted work. Dr. Kwatra, Dr. Dhar, Mr. Mukendi, Mr. Nana, Dr. Ngorima-Mabhena, and Dr. Mutevedzi report grants from the Bill & Melinda Gates Foundation during the conduct of the study. Mr. Welch shareholdings in Adcock Ingram Holdings Ltd, Aspen Pharmacare Holdings Ltd, Dischem Pharmacies Ltd, Discovery Ltd, and Netcare Ltd, outside the submitted work.

Dr. Myers, Dr. Jassat, and Dr. Blumberg have nothing to disclose.

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TABLES

Table 1: Seroprevalence of SARS-CoV-2 anti-spike or anti-nucleocapsid immunoglobulin G and factors associated with seropositivity in Gauteng Province, stratified by gender, age group, and district

Category	No. (%)	Seroprevalence, no. (%) [95% CI]	Odds ratio (95%CI)	Adjusted odds ratio‡ (95%CI)
All participants	7010 (100)	5125 (73.1) [72.0–74.1]	Not applicable	Not applicable
Gender	n = 7010			
Male	2941 (42.0)	1998 (67.9) [66.2–69.6]	Reference	Reference
Female	4065 (58.0)	3125 (76.9) [75.5–78.1]	1.56 (1.41–1.74)	1.43 (1.27–1.62)
Not reported	4			
Age group – yr*	n = 7010			
<12	753 (10.7)	423 (56.2) [52.6–59.7]	Reference	Not applicable
12–18	622 (8.9)	459 (73.8) [70.2–77.1]	2.20 (1.75–2.76)	Not applicable
>18 to 50	4047 (57.7)	2978 (73.6) [72.2–74.9]	2.17 (1.85–2.55)	Not applicable
>50	1588 (22.7)	1265 (79.7) [77.6–81.5]	3.05 (2.52–3.68)	Not applicable
Vaccination status*	n = 7010			
Not vaccinated	5691 (81.2)	3895 (68.4) [67.2–69.6]	Reference	Not applicable
Vaccinated	1319 (18.8)	1228 (93.1) [91.6–94.3]	6.22 (4.99–7.75)	Not applicable

Category	No. (%)	Seroprevalence, no. (%) [95% CI]	Odds ratio (95%CI)	Adjusted odds ratio‡ (95%CI)
Vaccination by age group	n = 7010			
<12 vaccinated	0	0	Not evaluable	Not evaluable
<12 unvaccinated	753 (10.7)	423 (55.8) [52.2–59.4]	0.56 (0.48–0.66)	0.63 (0.38–1.07)
12–18 unvaccinated	603 (8.6)	443 (73.5) [69.8–76.8]	1.21 (1.00–1.47)	1.29 (0.81–2.06)
12–18 vaccinated	19 (0.3)	16 (84.2) [60.8–94.8]	2.34 (0.68–8.03)	2.25 (0.61–8.33)
>18 to 50 unvaccinated	3356 (47.9)	2334 (69.5) [68.0–71.1]	Reference	Reference
>18 to 50 vaccinated	691 (9.9)	643 (93.1) [90.9–94.7]	5.87 (4.34–7.94)	5.69 (4.18–7.75)
>50 unvaccinated	979 (14.0)	695 (71.0) [68.1–73.7]	1.07 (0.92–1.25)	1.07 (0.90–1.27)
>50 vaccinated	609 (8.7)	569 (93.4) [91.2–95.1]	6.23 (4.48–8.65)	5.92 (4.21–8.33)
Reported previous covid-19 positive test	n = 7010			
Never tested	5956 (85.0)	4272 (71.7) [70.6–72.8]	Reference	Reference
Tested positive	195 (2.8)	172 (88.2) [82.9–92.0]	2.94 (1.90–4.57)	1.94 (1.23–3.08)
Tested negative	859 (12.3)	681 (79.3) [76.3–81.8]	1.50 (1.26–1.79)	0.95 (0.78–1.15)
Median household members per room	1 (0.5–1.5)		1.04 (0.96–1.09)	0.96 (0.91–1.00)
(IQR) – no.				
Occupation	n = 7010			

Category	No. (%)	Seroprevalence, no. (%) [95% CI]	Odds ratio (95%CI)	Adjusted odds ratio‡ (95%CI)
Unemployed	4102 (58.5)	3014 (73.5) [72.1–74.8]	Reference	Reference
Production sector	381 (5.4)	279 (73.2) [68.6–77.4]	0.99 (0.78–1.25)	1.18 (0.92–1.52)
Teacher, public transport, retail shop	661 (9.4)	509 (77.0) [73.6–80.1]	1.21 (1.00–1.47)	1.13 (0.92–1.39)
Healthcare worker	73 (1.0)	63 (86.3) [76.4–92.5]	2.27 (1.16–4.45)	1.73 (0.86–3.48)
Office work/Other	353 (5.0)	277 (78.5) [73.9–82.4]	1.32 (1.01–1.71)	1.18 (0.89–1.56)
Student	1440 (20.5)	981 (68.1) [65.7–70.5]	0.77 (0.68–0.88)	1.08 (0.90–1.30)
Smoking status†	n = 5740			
Non-smoker	4168 (59.5)	3234 (77.6) [76.3–78.8]	Reference	Reference
Daily	1125 (16.1)	748 (66.5) [63.7–69.2]	0.57 (0.50–0.66)	0.69 (0.59–0.80)
Once or twice a week	244 (3.5)	181 (74.2) [68.3–79.3]	0.83 (0.62–1.12)	1.07 (0.79–1.45)
Occasionally	203 (2.9)	157 (77.3) [71.1–82.6]	0.99 (0.70–1.38)	1.10 (0.78–1.56)
Comorbidities	n = 7010			
None	4731 (67.5)	3507 (74.1) [72.9–75.4]	Reference	Reference
1 or more	2279 (32.5)	1616 (70.9) [69.0–72.7]	0.85 (0.76–0.95)	1.06 (0.87–1.28)
HIV status	n = 7010			
HIV negative	6 460 (92.2)	4727 (73.2) [72.1–74.2]	Reference	Reference

Category	No. (%)	Seroprevalence, no. (%) [95% CI]	Odds ratio (95%CI)	Adjusted odds ratio‡ (95%CI)
HIV positive	550 (7.8)	396 (72.0) [68.1–75.6]	0.94 (0.78–1.14)	0.73 (0.59–0.90)
Dwelling type	n = 7010			
Formal stand-alone house	4700 (67.0)	3489 (74.2) [72.9–75.4]	Reference	Reference
Informal dwelling	1147 (16.4)	761 (66.3) [63.6–69.0]	0.68 (0.60–0.79)	0.78 (0.67–0.90)
Block of flats/ high-rise buildings	423 (6.0)	329 (77.8) [73.6–81.5]	1.22 (0.96–1.55)	1.33 (1.03–1.71)
Subsidized low-income housing	666 (9.5)	495 (74.3) [70.8–77.4]	1.00 (0.83–1.21)	0.98 (0.80–1.20)
Other	74 (1.1)	51 (68.9) [57.5–78.4]	0.77 (0.47–1.27)	0.81 (0.48–1.37)
District	n = 7010			
Johannesburg	2468 (35.2)	1881 (76.2) [74.5–77.8]	Reference	Reference
Ekurhuleni	1861 (26.5)	1382 (74.3) [72.2–76.2]	0.90 (0.78–1.04)	0.94 (0.81–1.09)
Sedibeng	564 (8.0)	397 (70.4) [66.5–74.0]	0.74 (0.61–0.91)	0.77 (0.62–0.95)
City of Tshwane	1464 (20.9)	976 (66.7) [54.2–69.0]	0.62 (0.54–0.72)	0.62 (0.53–0.72)
West Rand	653 (9.3)	489 (74.9) [71.4–78.1]	0.93 (0.76–1.14)	0.95 (0.77–1.18)

CI, confidence interval. IQR, interquartile range. *Age and vaccination status were not included in the regression model; instead, we introduced an interaction term between age and vaccination status to account for the differences in seroprevalence by vaccination status across the different age categories. †Smoking status was restricted to individuals aged >18 years in the univariable analyses. ‡We determine factors associated with SARS-CoV-2 seropositivity by multivariable logistic regression, adjusting for gender, age, comorbidities, employment, and district. Variables significant at p=0.15 in the univariable analysis were systematically added to the multivariable model assessing the model log likelihood and χ^2 . We showed decreased odds of SARS-

CoV-2 seropositivity in males, HIV-positive individuals, and individuals residing in Tshwane and Sedibeng. Vaccination status was obtained from vaccination certificates in 1026 of 1327 (77.3%) individuals who reported being vaccinated. Vaccination status and dwelling type were strongly associated with seropositivity. Unadjusted and adjusted odds ratios are presented with 95% confidence intervals (CI) in brackets. We used the national census classification to define dwelling types.

Table 2: Cumulative reported Covid-19 cases, hospitalizations, recorded deaths, and excess mortality in Gauteng Province by Covid-19 wave.

	Wave 1*	Wave 2*	Wave 3*	Wave 4*	TOTAL
Period for case wave	May 22–Sept 9, 2020	Nov 30, 2020–Mar 6, 2021	May 2–Sept 22, 2021	Nov 15–December 15, 2021	
Dominant variant	Wild type	Beta	Delta	Omicron	
Cases in wave†	211,220	171,559	490,460	164,911	1,038,150
Cases in first 31 days	19,820	52,061	38,577	164,911	275,369
Hospitalizations in first 31 days‡	2006	15,102	10,088	3432	30,628
Cumulative reported deaths in first 31 days§	249	636	668	194	1,747
Cumulative excess deaths in first 31 days¶	4,774	912	2650	569	8,905

*Case wave periods exclude inter-wave case numbers; other waves are lagged with respect to cases. Wave 4 is ongoing.

†Changes in testing rates, particularly the lower rates during Wave 1 due to constraints in laboratory capacity and prioritization of testing for hospitalized individuals, prevent direct comparisons, especially in terms of case numbers during the first wave in relation to the subsequent waves. Cases include asymptomatic and symptomatic individuals. Cumulative reported cases were sourced from the National Department of Health.¹³

‡Hospitalization data are from DATCOV, hosted by the National Institute for Communicable Disease,¹⁵ as described previously.³⁰ The system was developed during the course of the first wave, with gradual onboarding of facilities; hence, these data could underestimate hospitalized cases in the first wave relative to subsequent waves. The hospitalized cases include individuals with Covid-19, as well as coincidental infections identified as part of routine testing for SARS-CoV-2 of individuals admitted to the facilities to assist in triaging of patients in the hospital.

[§]Cumulative reported deaths were sourced from the National Department of Health.¹³

[¶]Excess mortality from natural causes was sourced from the South African Medical Research Council. The excess mortality data are reported through to December 4, 2021.

Figure 1: Flow of households and participants included in the seroprevalence survey.

This figure illustrates the flow of participants included in the present survey (survey 2) compared to survey 1,⁸ from approaching the individuals and negotiating participation through to specimen collection and processing.

Absolute numbers are presented. The final analysis included 7010 individuals in 26 sub-districts.

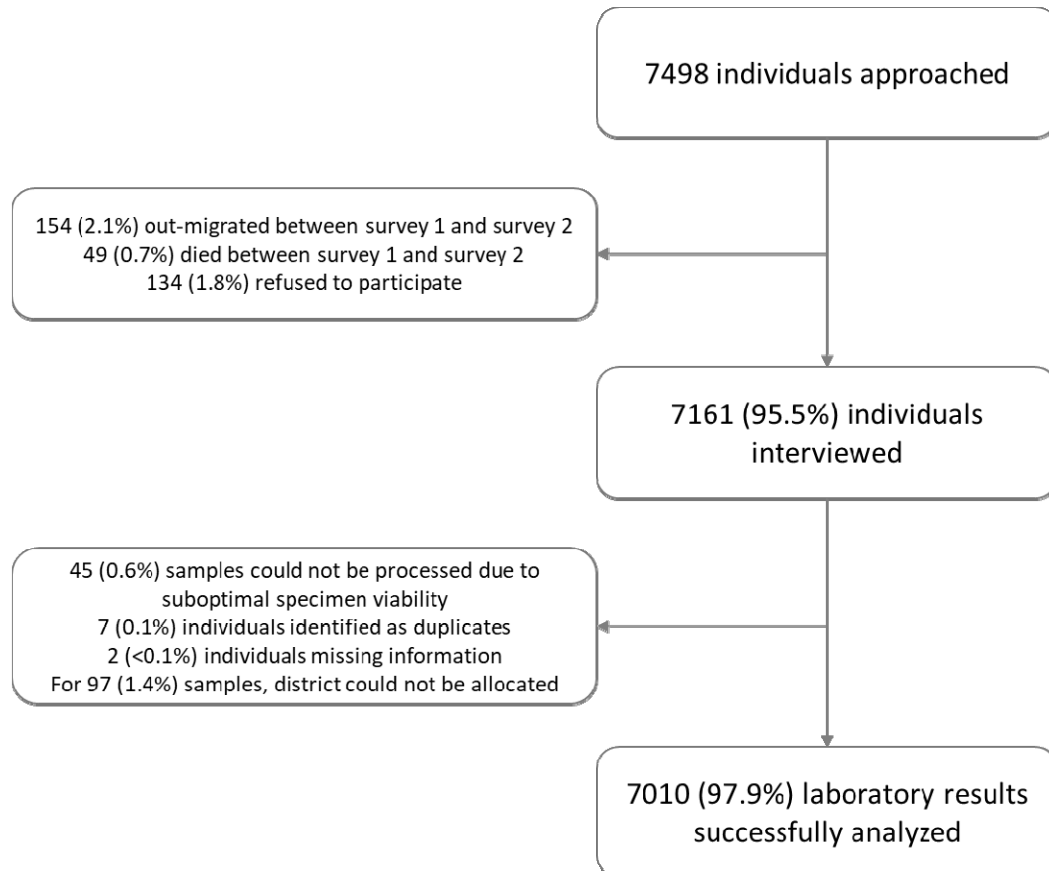


Figure 2: Seroprevalence across sub-districts in Gauteng Province.

Sampling period from October 22, 2021 through to December 9, 2021.

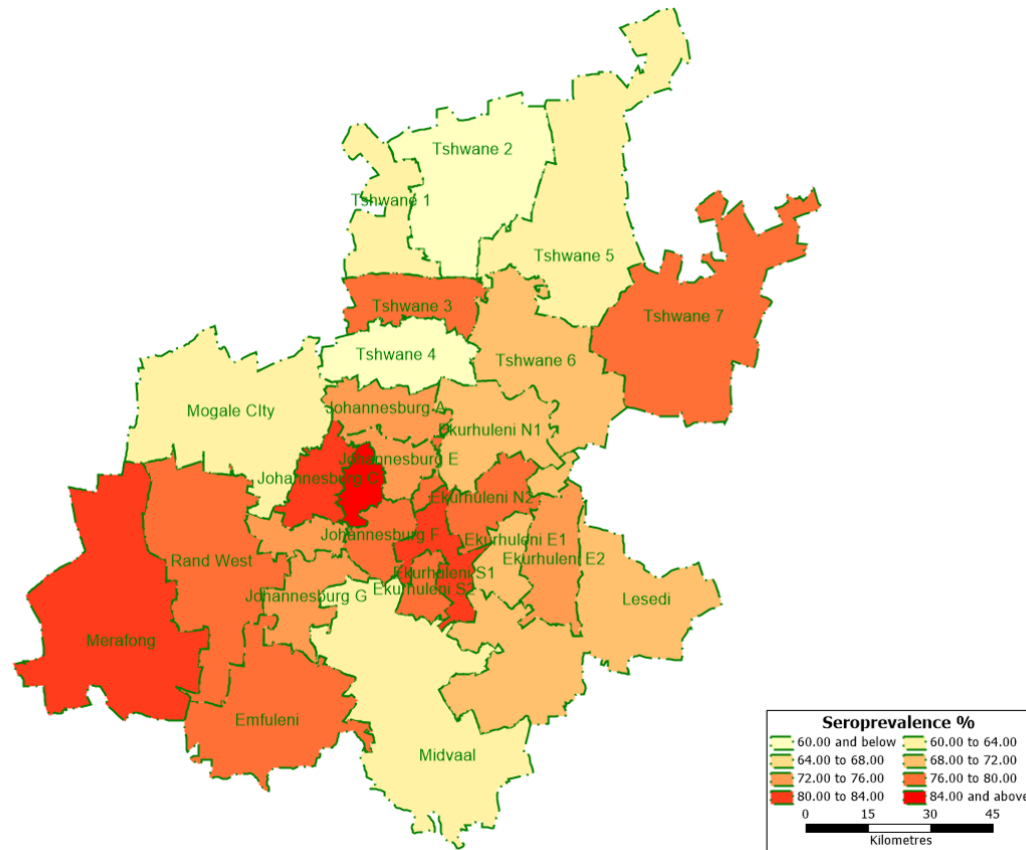
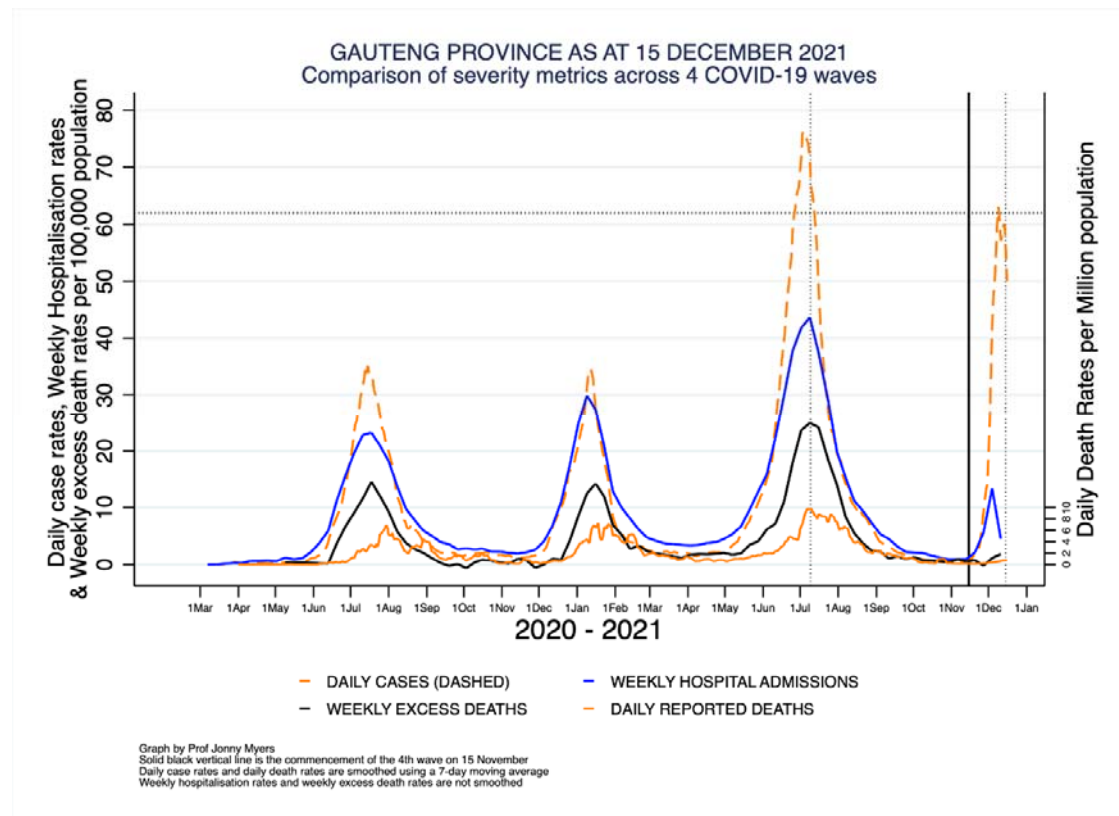


Figure 3: Covid-19 daily case rates, weekly hospital admission rates, weekly excess death rates, and daily reported death rates over the time period of the pandemic in Gauteng Province, South Africa



The daily rates are smoothed using a 7-day moving average while the weekly rates are unsmoothed. Hospital admissions data in Gauteng Province were provided by the National Institute of Communicable Diseases.¹⁵ Daily case and daily death data were sourced from the South African national coronavirus database produced by the National Department of Health.¹³ Weekly excess death data were sourced from the South African Medical Research Council weekly report for epidemiological week 48.¹⁴