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### **Article:**

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# Comparing Prospective Incident Severe Acute Respiratory Syndrome Coronavirus 2 Infection Rates During Successive Waves of Delta and Omicron in Johannesburg, South Africa

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In high-risk individuals in Johannesburg, during the Delta coronavirus disease 2019 wave, 22% (125/561) were positive, with 33% symptomatic (2 hospitalizations; 1 death). During Omicron, 56% (232/411) were infected, with 24% symptomatic (no hospitalizations or deaths). The remarkable speed of infection of Omicron over Delta poses challenges to conventional severe acute respiratory syndrome coronavirus 2 control measures.

**Keywords.** COVID-19; SARS-CoV-2; Delta; Omicron; South Africa.

Omicron (B.1.1.529) was designated the fifth severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant of concern in November 2021 by the World Health Organization (WHO) [1]. When first reported on 25 November 2021 in

South Africa, apprehension was expressed at the large number of mutations, putatively associated with antibody invasiveness, increased infectiousness, and transmissibility compared with other variants and wild-type virus [1–6]. Omicron subsequently become globally widespread [6–8]. Early reports indicated that infection with Omicron is associated with less hospitalization and mortality than the wild-type, Beta, or Delta variants, albeit occurring at a different stage of the pandemic and different levels of immunity following past infections and SARS-CoV-2 vaccine rollout [9–12].

We report clinical data from the COVER study, a 24-week prospective trial evaluating repurposed drugs for the prevention of SARS-CoV-2, sampling patients monthly for SARS-CoV-2 infection (NCT04561063). We take advantage of the study, conducted in Gauteng Province, South Africa, the initial epicenter of Omicron infections, to present an exploratory analysis of infection incidence and clinical findings for the overall cohort over 2 variant waves: Delta and Omicron.

## METHODS

COVER commenced in December 2020, at the end of the Beta wave in South Africa, approximately 6 months prior to the Delta wave. The 3-arm randomized study, conducted in inner-city Johannesburg, enrolled healthcare workers and those assessed as high risk for SARS-CoV-2 infection who had no evidence of current or previous coronavirus disease 2019 (COVID-19) infection (by symptoms or polymerase chain reaction [PCR] and/or serological evidence) and who were not vaccinated against SARS-CoV-2. The primary objective was to compare the efficacy of repurposed drugs in preventing SARS-CoV-2 (see [Supplementary Material](#) for the protocol). The trial was approved by an institutional review board, relevant local health bodies, and the WHO's ad hoc ethics review committee for COVID-19, and conforms to all international and South African legally mandated research requirements [13]. The results from COVER showed no significant effect of the experimental treatments on the risk of infection (results awaiting publication separately). Of note, while COVID-19 vaccination was an exclusion criterion at enrollment, as the availability of vaccines increased, individuals within the study were not prohibited from vaccination.

During the study, participants were followed for a maximum of 24 weeks, and those whose investigational product had been stopped (for reasons of vaccination, toxicity, or other reasons) were encouraged to remain as part of the cohort, with the same monitoring protocol. Routine in-clinic follow-up visits were conducted every 4 weeks for all individuals until the end of the study, including PCR and antibody serology testing

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(Orient Gene, BHA Medical). Where participants had suggestive COVID-19 symptoms outside of this testing schedule, additional PCR tests were performed. Weekly check-ins were conducted telephonically or using internet-based communication systems to assess for COVID-19–related symptoms. Secondary endpoints included symptoms assessed through FLU-PRO Plus (successfully used in other COVID-19 studies) [14–16]. Multiple, discrete occurrences of COVID-19 infection could be identified in a single participant.

The current study uses the pooled data collected in COVER to assess laboratory-confirmed COVID-19 infections. We compare infection rate and clinical characteristics across participants with infections in the Delta versus Omicron waves. The beginning of November 2021 was used as the cutoff to define the distinct waves for inclusion dates of 8 December 2020 (enrollment start) through 31 October 2021 for the Delta wave and 1 November through 24 January 2022 (data cutoff) for the Omicron wave. The cutoff was selected as Omicron was identified in late November, suggesting very low levels of circulating Omicron prior to this, and indicating that infections prior to this date were most likely Delta [5, 11, 17, 18]. Despite a low number of infections recorded in the beginning of the study, we acknowledge that Beta was likely the predominant variant

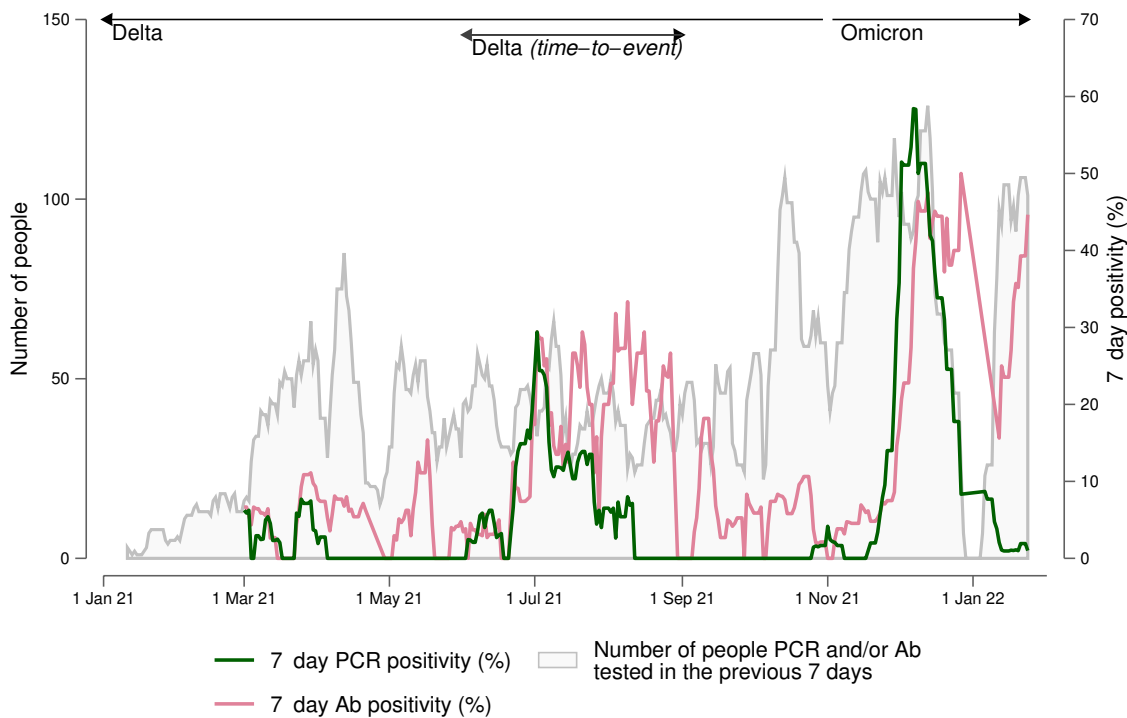
in early 2021. Accordingly, in the time-to-event analysis, we present a more precise analysis for the Delta wave using inclusion dates of 1 June–31 August 2021.

Participants eligible for inclusion were those randomized with at least 1 follow-up visit in either of the waves; participants could be included in both waves depending on their time of enrollment. More detailed information on ascertainment of COVID-19 infections, reinfections, and the statistical methods used are provided in the [Supplementary Appendix](#).

## RESULTS

Overall, 1716 participants were screened between December 2020 and November 2021, of which 828 were enrolled. Of these, 561 individuals had at least 1 follow-up visit during Delta and 411 individuals had follow-up during Omicron; 263 had at least 1 follow-up visit in both periods ([Supplementary Figure 1](#)).

The 2 groups were not part of any randomization; thus, they differed in terms of baseline characteristics. In general, the cohort was young with few self-reported comorbidities; individuals in the Omicron wave tended to be younger with fewer comorbidities and differed in their occupation, reflective of differing recruitment strategies over time ( $P < .01$  for all



**Figure 1.** Number of people receiving a polymerase chain reaction (PCR) or antibody (Ab) test and 7-day test positivity. Shown are the number of participants who received a PCR or Ab test in the previous 7 days (inclusive), and the percentage of those who have at least 1 positive coronavirus disease 2019 test result in the same 7-day period. The green line shows PCR results only. The pink line shows Ab results only. Data are shown by specimen date (ie, the date the sample was collected). Participants tested more than once in the period are only counted once in the denominator. Participants with >1 positive test result in the period are only included once in the numerator. Any antibody test results after the first positive Ab test for a participant are excluded; all Ab test results after on-study vaccination are excluded.

comparisons; [Supplementary Table 1](#)). Overall, 20% of the population received a COVID-19 vaccination while in follow-up; these were both the Ad26.COV2.S (J&J) single and the BNT162b2 (Pfizer-BioNTech) 2-dose regimen. Follow-up was longer in the Delta wave versus the Omicron wave; 68 participants included in the Delta wave entered Omicron with evidence of previous infection or having received a SARS-CoV-2 vaccine.

[Figure 1](#) shows the SARS-CoV-2 infections over the course of the study. [Figure 2](#) presents the time-to-event analysis, showing a significantly higher probability of event in the Omicron wave compared to the Delta wave. Overall, 125 of 561 (22% [95% confidence interval {CI}, 18.9%–26.0%]) participants in the Delta wave had a confirmed infection; 5 participants had reinfection within the Delta wave for a total of 130 infections (reinfection defined as per the [Supplementary Appendix](#)). In the Omicron wave, 232 of 411 (56% [95% CI, 51.5%–61.3%]) participants had a confirmed infection (with 1 additional assumed reinfection likely to have been due to a false-negative antibody test at screening). Most infections in the Delta wave were identified by serology only (80/130 [62%]) compared to 34% (79/233) during Omicron ([Figure 1](#)).

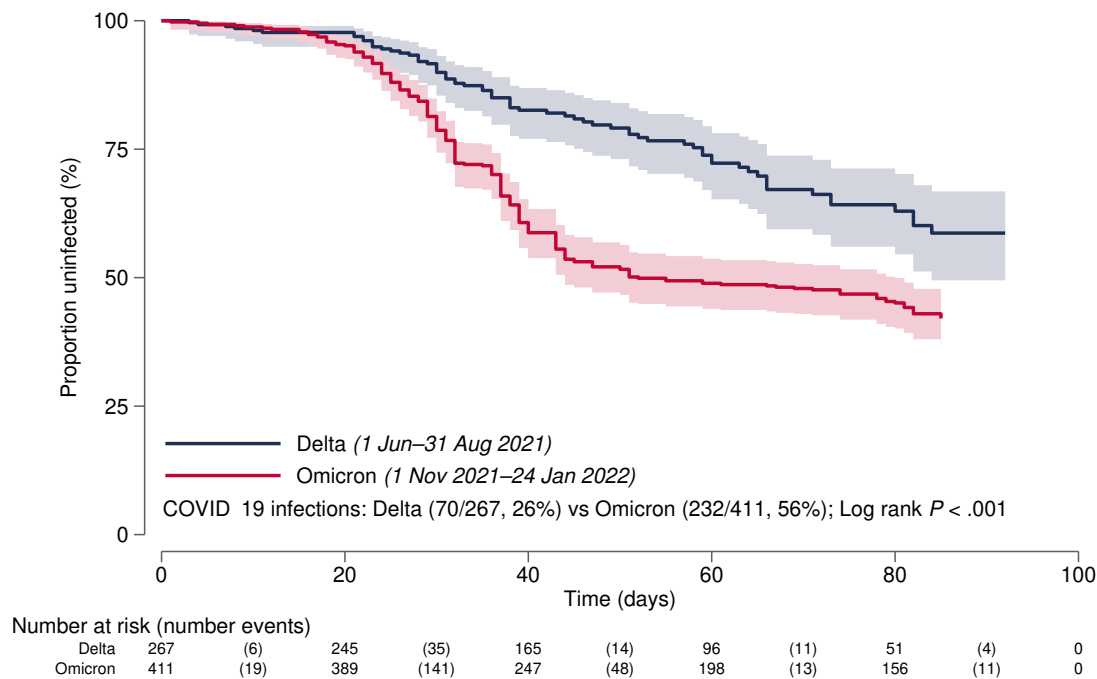
We did not confirm the Delta wave infections as sequencing was not available; for Omicron, S gene-target failure was used

as a proxy marker on samples collected over 5 days in November, which confirmed that all samples assessed were Omicron. Country monitoring of both Delta and Omicron confirmed that each overwhelmingly predominated during each of our defined timelines [5, 17, 18].

Most Omicron infections were asymptomatic (176/233 [76%]), compared to 67% (87/130) during Delta. Two participants were hospitalized because of COVID-19, and 1 died; both were in the Delta wave. Of the symptomatic infections, 48 had at least 1 completed FLU-PRO questionnaire ( $n = 19$  Delta wave and  $n = 29$  Omicron wave). In those with symptoms, these were less severe with Omicron than with Delta ([Supplementary Figure 2](#) and [Supplementary Table 2](#)).

## DISCUSSION

We show unprecedented spread of SARS-CoV-2 infection at the site of Omicron's original identification. In this cohort, 56% were infected within just 12 weeks of Omicron, most in the first 3 weeks, and most asymptomatic, when measured against the Delta variant, which itself spread quickly and widely. The usual strategies and policies around isolation, contact tracing, and subsequent quarantining, often relying on clinical symptoms, would likely have limited impact in curbing



**Figure 2.** Kaplan-Meier plots for time to infection by wave. Data are time to infection (defined as positive polymerase chain reaction and/or antibody at any visit) in each wave where the Delta wave was defined as 1 June to 31 August 2021 and the Omicron wave was defined as 1 November 2021 to 24 January 2022 (data cutoff). Participants became at risk at the start of the wave or at their enrollment date, whichever was later. Participants without infection were censored at their final study visit or the end of the wave, whichever was earlier. The number of infections for the Delta wave presented on the figure do not match the main text due to differences in wave inclusion date definition (the time-to-event analysis uses a more precise window). Abbreviation: COVID-19, coronavirus disease 2019.

spread in the face of such a rapid and vast surge of largely asymptomatic transmission. Many countries pursued emergency vaccination of targeted groups, urgent lockdowns with different restrictive measures, and other containment strategies in anticipation that local immunity may be insufficient against an Omicron wave. Whether these measures altered the natural course of the Omicron outbreak is a critically important public health, political, and economic global question.

In a population with no evidence of previous infection and no COVID-19 vaccinations on enrollment, the study shows very limited severity of Omicron infection with no serious Omicron-related clinical events. This finding is likely even more favorable for a population that has substantial preexisting immunity or high levels of vaccination. Despite showing a low risk of severe infection, the population examined was young with a lower baseline risk than other populations and so results from our cohort may not be translatable to older populations with higher levels or different comorbidities [19].

There are limitations to this analysis, although it is uncertain how these factors impact meaningfully on susceptibility to infection. Foremost, the heterogeneity of the cohort across waves may impact interpretation. SARS-CoV-2 infection has almost disappeared in Gauteng by mid-January 2022, but more infections, hospitalizations or deaths may accumulate beyond the time frame of our analysis [20]. The serology tests used may have resulted in false-negative/positive results, meaning some infections may have been unidentified. We may have mischaracterized variants, although very few infections were detected when Beta was circulating, suggesting minimal overlap, and while S-gene target failure cases have been seen in Delta cases, country monitoring suggests almost complete displacement of Delta by Omicron. There was no effect of the study drugs on overall infection rates. Contextual social issues, including lockdown/quarantine intensity (although largely similar within Gauteng during Delta and Omicron), behavioral characteristics (eg, social gatherings, mask usage), and the intense social violence that occurred within Gauteng at the end of the Delta wave, may have altered transmission patterns [11, 12].

Our cohort, with no prior reported infection, no PCR or serological evidence of recent infection, and low levels of vaccination, was infected swiftly and largely asymptotically. This has profound public health consequences for spread of the Omicron variant and traditional measures of containment.

### Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

**Patient consent.** All patients' written consent was obtained. The trial was approved by an institutional review board, relevant local health bodies, and the World Health Organization's ad hoc Ethics Review Committee for COVID-19, and conforms to all international and South African legally mandated research requirements.

**Financial support.** This work was supported by Unitaid.

**Potential conflicts of interest.** The authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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## CONFIDENCE IN DOVATO ACROSS TREATMENT SETTINGS<sup>4-9</sup>

Treatment-naïve resistance rates, with up to **3 years** of evidence<sup>5-7</sup>

**0%**  
(n=0/1,885)<sup>\*4</sup>  
REAL-WORLD EVIDENCE

**0.1%**  
(n=1/953)<sup>\*\*1,11,5,5-7</sup>  
RANDOMISED CONTROLLED TRIALS

Treatment-experienced resistance rates, with up to **5 years** of evidence<sup>1-3</sup>

**0.03%**  
(n=10/35,888)<sup>\*4</sup>  
REAL-WORLD EVIDENCE

**0%**  
(n=0/615)<sup>11,5,8,9</sup>  
RANDOMISED CONTROLLED TRIALS

## >300,000 PEOPLE LIVING WITH HIV HAVE BEEN TREATED WITH DOVATO GLOBALLY<sup>10</sup>

DOVATO is supported by a wealth of evidence, with the outcomes of **>40,000** people living with HIV captured within clinical trials and real-world evidence, including those with:<sup>4-9,11,12</sup>



**NO PRIOR TREATMENT EXPERIENCE<sup>13</sup>**



**NO BASELINE RESISTANCE TESTING<sup>13</sup>**



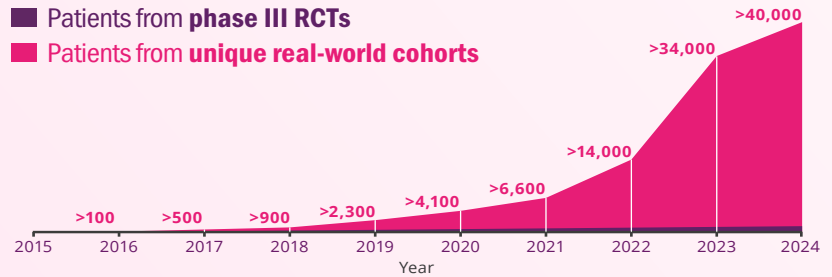
**HIGH BASELINE VIRAL LOAD**  
(>100,000 copies/mL and even >1M copies/mL)<sup>6,13</sup>



**LOW CD4 + COUNT**  
(≤200 cells/mm<sup>3</sup>)<sup>13</sup>

■ Patients from phase III RCTs

■ Patients from unique real-world cohorts



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### ABBREVIATIONS

**3TC**, lamivudine; **CD4**, cluster of differentiation 4; **DTG**, dolutegravir; **FDA**, United States Food and Drug Administration; **FTC**, emtricitabine; **HIV**, human immunodeficiency virus; **ITT-E**, intention-to-treat exposed; **NRTI**, nucleoside/nucleotide reverse transcriptase inhibitor; **RCT**, randomised controlled trial; **RNA**, ribonucleic acid; **TAF**, tenofovir alafenamide fumarate; **TDF**, tenofovir disoproxil fumarate; **XTC**, emtricitabine.

### FOOTNOTES

\*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

\*\*The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).<sup>5-7</sup>

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).<sup>13</sup>

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.<sup>6</sup>

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.<sup>7</sup> Results at week 24 of the study.

|| The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).<sup>8,9</sup>

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).<sup>8,13</sup>

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).<sup>9</sup>