SARS-CoV-2 reinfection trends in South Africa: analysis of routine surveillance data

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Abstract

Objective To examine whether SARS-CoV-2 reinfection risk has changed through time in South Africa, in the context of the emergence of the Beta and Delta variants

Design Retrospective analysis of routine epidemiological surveillance data

Setting Line list data on SARS-CoV-2 with specimen receipt dates between 04 March 2020 and 30 June 2021, collected through South Africa’s National Notifiable Medical Conditions Surveillance System

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Participants 1,551,655 individuals with laboratory-confirmed SARS-CoV-2 who had a positive test result at least 90 days prior to 30 June 2021. Individuals having sequential positive tests at least 90 days apart were considered to have suspected reinfections.

Main outcome measures Incidence of suspected reinfections through time; comparison of reinfection rates to the expectation under a null model (approach 1); empirical estimates of the time-varying hazards of infection and reinfection throughout the epidemic (approach 2)

Results 16,029 suspected reinfections were identified. The number of reinfections observed through the end of June 2021 is consistent with the null model of no change in reinfection risk (approach 1). Although increases in the hazard of primary infection were observed following the introduction of both the Beta and Delta variants, no corresponding increase was observed in the reinfection hazard (approach 2). Contrary to expectation, the estimated hazard ratio for reinfection versus primary infection was lower during waves driven by the Beta and Delta variants than for the first wave (relative hazard ratio for wave 2 versus wave 1: 0.75 (CI<sub>95</sub>: 0.59-0.97); for wave 3 versus wave 1: 0.70 (CI<sub>95</sub>: 0.55-0.90)). Although this finding may be partially explained by changes in testing availability, it is also consistent with a scenario in which variants have increased transmissibility but little or no evasion of immunity.

Conclusion We conclude there is no population-wide epidemiological evidence of immune escape and recommend ongoing monitoring of these trends.

Box 1

What is already known on this topic

• Prior infection with SARS-CoV-2 is estimated to provide at least an 80% reduction in infection risk (1,2).

• Laboratory-based studies indicate reduced neutralization by convalescent serum for the Beta and Delta variants relative to wild type virus (3–6); however, the impact of these reductions on risk of reinfection is not known.
What this study adds

- We provide two methods for monitoring reinfection trends to identify signatures of changes in reinfection risk.
- We find no evidence of increased reinfection risk associated with circulation of Beta or Delta variants compared to the ancestral strain in routine epidemiological data from South Africa.

Introduction

As of 30 June 2021, South Africa had more than two million cumulative laboratory-confirmed cases of SARS-CoV-2, concentrated in three waves of infection. The first case was detected in early March 2020 and was followed by a wave that peaked in July 2020 and officially ended in September. The second wave, which peaked in January 2021 and ended in February, was driven by the Beta (B.1.351 / 501Y.V2 / 20H) variant, which was first detected in South Africa in October 2020 (7). The third wave, which peaked in July and ended in September 2021, was dominated by the Delta (B.1.617.2 / 478K.V1 / 21A) variant (8).

Following emergence of the Beta and Delta variants of SARS-CoV-2 in South Africa, a key question remains of whether there is epidemiologic evidence of increased risk of SARS-CoV-2 reinfection with these variants (i.e., immune escape). Laboratory-based studies suggest that convalescent serum has a reduced neutralizing effect on these variants compared to wild type virus in vitro (3–6); however, this finding does not necessarily translate into immune escape at the population level.

To examine whether reinfection risk has changed through time, it is essential to account for potential confounding factors affecting the incidence of reinfection: namely, the changing force of infection experienced by all individuals in the population and the growing number of individuals eligible for reinfection through time. These factors are tightly linked to the timing of epidemic waves. We examine reinfection trends in South Africa using two approaches that account for these factors to address the question of whether circulation of
the Beta or Delta variants was associated increased reinfection risk, as would be expected if their emergence was driven by immune escape.

Methods

Data sources
Data analysed in this study come from two sources maintained by the National Institute for Communicable Diseases (NICD): the outbreak response component of the Notifiable Medical Conditions Surveillance System (NMC-SS) deduplicated case list and the line list of repeated SARS-CoV-2 tests. All positive tests conducted in South Africa appear in the combined data set, regardless of the reason for testing or type of test (PCR or antigen detection).

Civil unrest during July 2021 severely disrupted testing in Gauteng and KwaZulu-Natal, the two most populous provinces in the country. As a result, case data became unreliable and a key assumption of our models - that the force of infection is proportional to the number of positive tests - was violated. Increasing vaccination rates from August 2021 could also introduce bias. We therefore limited the analysis to data with specimen receipt dates between 04 March 2020 and 30 June 2021.

A combination of deterministic (national ID number, names, dates of birth) and probabilistic linkage methods were utilized to identify repeated tests conducted on the same person. In addition, provincial COVID-19 contact tracing teams identify and report repeated SARS-Cov-2 positive tests to the NICD, whether detected via PCR or antigen tests. The unique COVID-19 case identifier which links all tests from the same person was used to merge the two datasets. Irreversibly hashed case IDs were generated for each individual in the merged data set.

Primary infections and suspected repeat infections were identified using the merged data set. Repeated case IDs in the line list were identified and used to calculate the time
between consecutive positive tests for each individual, using specimen receipt dates. If the time between sequential positive tests was at least 90 days, the more recent positive test was considered to indicate a suspected new infection. We present a descriptive analysis of suspected third infections, although only suspected second infections (which we refer to as “reinfections”) were considered in the analyses of temporal trends. Incidence time series for primary infections and reinfections are calculated by specimen receipt date of the first positive test associated with the infection, and total observed incidence is calculated as the sum of first infections and reinfections. The specimen receipt date was chosen as the reference point for analysis because it is complete within the data set.

All analyses were conducted in the R statistical programming language (R version 4.0.5 (2021-03-31)).

Data validation
To assess validity of the data linkage procedure and thus verify whether individuals identified as having suspected reinfections did in fact have positive test results at least 90 days apart, we conducted a manual review of a random sample of suspected second infections occurring on or before 20 January 2021 (n=585 of 6017; 9.7%). This review compared fields not used for linkages (address, cell-phone numbers, email addresses, facility, and health-care providers) between records in the NMC-SS and positive test line lists. Where uncertainty remained and contact details were available, patients or next-of-kin were contacted telephonically to verify whether the individual had received multiple positive test results.

Descriptive analysis
We calculated the time between successive positive tests as the number of days between the last positive test associated with an individual’s first identified infection (i.e., within 90 days of a previous positive test, if any) and the first positive test associated with their suspected second infection (i.e., at least 90 days after the most recent positive test).
We also compared the age, gender, and province of individuals with suspected reinfections to individuals eligible for reinfection (i.e., who had a positive test result at least 90 days prior to 30 June 2021).

We did not calculate overall incidence rates by wave because the force of infection is highly variable in space and time, and the period incidence rate is also influenced by the temporal pattern of when people become eligible for reinfection. Incidence rate estimates would therefore be strongly dependent on the time frame of the analysis and not comparable to studies from other locations or time periods.

**Statistical analysis of reinfection trends**

We analysed the NICD national SARS-CoV-2 routine surveillance data to evaluate whether reinfection risk has changed since emergence of the Beta or Delta variants. We evaluated the daily numbers of suspected reinfections using two approaches. First, we constructed a simple null model based on the assumption that the reinfection hazard experienced by previously diagnosed individuals is proportional to the incidence of detected cases and fit this model to the pattern of reinfections observed before the emergence of the Beta variant (through 30 September 2020). The null model assumes no change in the reinfection hazard coefficient through time. We then compared observed reinfections after September 2020 to expected reinfections under the null model.

Second, we evaluated whether there has been a change in the *relative* hazard of reinfection versus primary infection, to distinguish between increased overall transmissibility of the variants and any *additional* risk of reinfection due to potential immune escape. To do this, we calculated an empirical hazard coefficient at each time point for primary infections and reinfections and compared their relative values through time.
Approach 1: Catalytic model assuming a constant reinfection hazard coefficient

Model description For a case testing positive on day $t$ (by specimen receipt date), we assumed the reinfection hazard is 0 for each day from $t + 1$ to $t + 90$ and $\lambda \hat{C}_\tau$ for each day $\tau > t + 90$, where $\hat{C}_\tau$ is the 7-day moving average of the detected case incidence (first infections and reinfections) for day $\tau$. The probability of a case testing positive on day $t$ having a diagnosed reinfection by day $x$ is thus $p(t, x) = 1 - e^{-\sum_{i=t+90}^{x} \lambda \hat{C}_i}$, and the expected number of cases testing positive on day $t$ that have had a diagnosed reinfection by day $x$ is $C^1_t p(t, x)$, where $C^1_t$ is the detected case incidence (first infections only) for day $t$. Thus, the expected cumulative number of reinfections by day $x$ is $Y_x = \sum_{t=0}^{x} C^1_t p(t, x)$. The expected daily incidence of reinfections on day $x$ is $D_x = Y_x - Y_{x-1}$.

Model fitting The model was fitted to observed reinfection incidence through 30 September 2020 assuming data are negative binomially distributed with mean $D_x$. The reinfection hazard coefficient ($\lambda$) and the inverse of the negative binomial dispersion parameter ($\kappa$) are fitted to the data using a Metropolis-Hastings Monte Carlo Markov Chain (MCMC) estimation procedure implemented in the R Statistical Programming Language. We ran 4 MCMC chains with random starting values for a total of 1e+05 iterations per chain, discarding the first 2,000 iterations (burn-in). Convergence was assessed using the Gelman-Rubin diagnostic (9).

Model-based projection We used 1,500 samples from the joint posterior distribution of fitted model parameters to simulate possible reinfection time series under the null model, generating 100 stochastic realizations per parameter set. We then calculated projection intervals as the middle 95% of daily reinfection numbers across these simulations.

We applied this approach at the national level, as well as to Gauteng, KwaZulu-Natal, and Western Cape Provinces, which were the only provinces with a sufficient number...
of reinfections during the fitting period to permit estimation of the reinfection hazard coefficient.

**Approach 2: Empirical estimation of time-varying infection and reinfection hazards**

We estimated the time-varying empirical hazard of infection as the daily incidence per susceptible individual. This approach requires reconstruction of the number of susceptible individuals through time. We distinguish between three “susceptible” groups: naive individuals who have not yet been infected \( (S_1) \), previously infected individuals who had undiagnosed infections \( (S_2^u) \), and previously infected individuals who had a prior positive test at least 90 days ago \( (S_2) \). We estimate the numbers of individuals in each of these categories on day \( t \) as follows:

\[
S_1(t) = N - \sum_{i=0}^{i=t} \frac{C_i}{p_{obs}}
\]

\[
S_2^u(t) = \frac{(1 - p_{obs})}{p_{obs}} \sum_{i=0}^{i=t} C_i
\]

\[
S_2(t) = \sum_{i=0}^{i=t-90} C_i - \sum_{i=0}^{i=t} \frac{X_i}{p_{obs_2}}
\]

where \( N \) is the total population size, \( C_i \) is the number of individuals with their first positive test on day \( i \), \( p_{obs} \) is the probability of detection for individuals who have not had a previously identified infection, \( p_{obs_2} \) is the probability of detection for individuals who have had a previously identified infection, and \( X_i \) is the number of individuals with a detected reinfection on day \( i \). For the main analysis, we assume \( p_{obs} = 0.1 \) and \( p_{obs_2} = 0.5 \), although the conclusions are robust to these assumptions (see Sensitivity Analysis).
Individuals in $S_2$ and $S_2'$ are assumed to experience the same daily hazard of reinfection, estimated as $h_2(t) = \frac{\dot{X}_t/p_{obs}}{S_2(t)}$. The daily hazard of infection for previously uninfected individuals is then estimated as $h_1(t) = \frac{c_t/p_{obs} - h_2 S_2^u(t)}{S_1(t)}$.

If we assume that the hazard of infection is proportional to incidence ($I_t$), $h_1(t) = \lambda_1(t)I_t$ and $h_2(t) = \lambda_2(t)I_t$, we can then examine the infectiousness of the virus through time as:

$$\lambda_1(t) = \frac{h_1(t)}{(c_t/p_{obs} + X_t/p_{obs_2})}$$

$$\lambda_2(t) = \frac{h_2(t)}{(c_t/p_{obs} + X_t/p_{obs_2})}$$

We also used this approach to construct a data set with the daily numbers of individuals eligible to have a suspected second infection ($S_2(t)$) and not eligible for suspected second infection ($S_1(t) + S_2^u(t)$) by wave. Wave periods were defined as the time surrounding the wave peak for which the 7-day moving average of case numbers was above 15% of the wave peak. We then analyzed these data using a generalized linear mixed model to estimate the relative hazard of infection in the population eligible for suspected second infection, compared to the hazard in the population not eligible for suspected second infection.

Our primary model was a Poisson model with a log link function, groupinc = Poisson($\mu$):

$log(\mu) \sim$ group $\times$ wave $+$ offset($log$(groupsize)) $+$ (day)

The outcome variable (groupinc) was the daily number of observed infections in the two groups. Our main interest for this analysis was in whether the relative hazard was higher in the second and third waves, thus potentially indicating immune escape. This effect
is measured by the interaction term between group and wave. The offset term is used to ensure that the estimated coefficients can be appropriately interpreted as \textit{per capita} rates.

We used day as a proxy for force of infection and reporting patterns and examined models where day was represented as a random effect (to reflect that observed days can be thought of as samples from a theoretical population) and as a fixed effect (to better match the Poisson assumptions). As focal estimates from the two models were indistinguishable, we present only the results based on the random effect assumption. Both versions of the model are included in the code repository.

**Results**

We identified 16,029 individuals with at least two suspected infections (through 30 June 2021) and 80 individuals with suspected third infections (Figure 1).
Figure 1. Daily numbers of detected primary infections, individuals eligible to be considered for reinfection, and suspected reinfections in South Africa. A: Time series of detected primary infections. Black line indicates 7-day moving average; black points are daily values. Colored bands represent wave periods, defined as the period for which the 7-day moving average of cases was at least 15% of the corresponding wave peak (purple = wave 1, pink = wave 2, orange = wave 3). B: Population at risk for reinfection (individuals whose most recent positive test was at least 90 days ago and who have not yet had a suspected reinfection). C: Time series of suspected reinfections. Blue line indicates 7-day moving average; blue points are daily values.

Data validation

Of the 585 randomly selected individuals with possible reinfections in the validation sample, 562 (96%) were verified as the same individual based on fields not used to create the linkages; the remaining 23 (4%) were either judged not a match or to have insufficient evidence (details captured by the clinician or testing laboratory) to determine whether the records belonged to the same individual.
Descriptive analysis

Time between successive positive tests

The time between successive positive tests for individuals with suspected reinfections was bimodally distributed with peaks near 180 and 360 days (Figure 2A). The shape of the distribution was strongly influenced by the timing of South Africa’s epidemic waves. The first peak corresponds to individuals initially infected in wave 1 and reinfected in wave 2 or initially infected in wave 2 and reinfected in wave 3, while the second peak corresponds to individuals initially infected in wave 1 and reinfected in wave 3.

Figure 2. Descriptive analysis of suspected reinfections. A: Time in days between infections for individuals with suspected reinfection. Note that the time since the previous positive test must be at least 90 days. B: Percentage of eligible primary infections with suspected reinfections, by province. C: Age distribution of individuals with suspected reinfections (blue) versus eligible individuals with no detected reinfection (yellow), by sex. Solid lines indicate females; dashed lines indicate males.
Distribution of suspected reinfections by province

Suspected reinfections were identified in all nine provinces (Figure 2B). The reinfection rate was highest in Gauteng, where 5,872 of 415,291 eligible primary infections (1.41%) had suspected reinfections and lowest in Eastern Cape (1,226 of 195,481; 0.63%). For comparison, the national reinfection rate was 195,481; 1.03% (16,029 of 1,551,655 eligible primary infections). Numbers for all provinces are provided in Table S1.

Breakdown of suspected reinfections by sex and age group

Among 1,518,044 eligible primary infections with both age and sex recorded, 9,413 of 877,676 females (1.07%) and 6,573 of 640,368 males (1.03%) had suspected reinfections. Relative to individuals with no identified reinfection, reinfections were concentrated in adults between the ages of 20 and 55 years (Figure 2C). Numbers for all age group-sex combinations are provided in Table S2.

Individuals with multiple suspected reinfections

80 individuals were identified who had three suspected infections. Most of these individuals initially tested positive during the first wave, with suspected reinfections associated with waves two and three (Figure S1). No individual had more than two suspected reinfections. Further details are given in the Supplementary Material (Table S1, Table S2, Figure S1).

Reinfection trends

The first individual became eligible for reinfection on 2020-06-02 (i.e., 90 days after the first case was detected). No suspected reinfections were detected until 23 June 2020, after which the number of suspected reinfections increased gradually. The 7-day moving average of suspected reinfections reached a peak of 162.4 during the second epidemic wave and a maximum of 304.6 during the third wave, as of 30 June 2021 (Figure 1).

Approach 1: Comparison of data to projections from the null model

Under the null model of no change in the reinfection hazard coefficient through time, the number of incident reinfections was expected to be low prior to the second wave and to
increase substantially during the second and third waves, peaking at a similar time to incident primary infections. The observed time series of suspected reinfections closely follows this pattern (Figure 3), although it falls slightly below the prediction interval toward the end of the time series. Provincial-level analyses suggest that this deviation is driven primarily by the Western Cape, where the observed time series of suspected reinfections falls below the prediction interval near the peak of both waves two and three (Figure S3). In contrast, the observed time series of suspected reinfections consistently falls within the prediction interval for Gauteng and KwaZulu-Natal (Figure S3). This pattern may result from policies implemented only in the Western Cape that limited testing during the wave peaks.

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Observed and expected temporal trends in reinfection numbers. Blue lines (points) represent the 7-day moving average (daily values) of suspected reinfections. Grey lines (bands) represent mean predictions (95% projection intervals) from the null model. A: The null model was fit to data on suspected reinfections through 2021-09-30, prior to the emergence of the Beta variant. B: Comparison of data to projections from the null model over the projection period.

**Approach 2: Empirical estimation of time-varying infection and reinfection hazards**

The estimated hazard coefficient for primary infection increases steadily through time, as expected under a combination of relaxing of restrictions, behavioural fatigue, and introduction of variants with increased transmissibility. The estimated hazard coefficient for reinfection, in contrast, remains relatively constant, with the exception of an initial spike in mid-2020, when reinfection numbers were very low. The mean ratio of reinfection hazard to
primary infection hazard has decreased slightly with each subsequent wave, from 0.15 in wave 1 to 0.12 in wave 2 and 0.1 in wave 3. The absolute values of the hazard coefficients and hazard ratio are sensitive to assumed observation probabilities for primary infections and reinfections; however, temporal trends are robust (Figure S5).

These findings are consistent with the estimates from the generalized linear mixed model based on the reconstructed data set. In this analysis, the relative hazard ratio for wave 2 versus wave 1 was 0.75 (CI$_{95}$: 0.59-0.97) and for wave 3 versus wave 1 was 0.70 (CI$_{95}$: 0.55-0.90).

![Figure 4. Empirical estimates of infection and reinfection hazards. A: Estimated time-varying hazard coefficients for primary infection (black) and reinfections (green). Colored bands represent wave periods, defined as the period for which the 7-day moving average of cases was at least 15% of the corresponding wave peak (purple = wave 1, pink = wave 2, orange = wave 3). B: Ratio of the empirical hazard for reinfections to the empirical hazard for primary infections.](image)

**Discussion**

Our analyses suggest that the cumulative number of reinfections observed through June 2021 is consistent with the null model of no change in reinfection risk through time. Furthermore, our findings suggest that the relative hazard of reinfection versus primary infection has decreased with each wave of infections, as would be expected if the risk of
primary infection increased without a corresponding increase in reinfection risk. Based on these analyses, we conclude there is no population-level evidence of immune escape at this time. We recommend ongoing monitoring of these trends.

Differences in the time-varying force of infection, original and subsequent circulating lineages, testing strategies, and vaccine coverage limit the usefulness of direct comparisons of rates of reinfections across countries or studies. Reinfection does however appear to be relatively uncommon. The PCR-confirmed reinfection rate ranged from 0% – 1.1% across eleven studies included in a systematic review (10). While none of the studies included in the systematic review reported increasing risk of reinfection over time, the duration of follow-up was less than a year and most studies were completed prior to the identification of the Beta and Delta variants of concern. Our findings are consistent with results from the PHIRST-C community cohort study conducted in two locations in South Africa, which found that infection prior to the second wave provided 84% protection against reinfection during the second (Beta) wave (11), comparable to estimates of the level of protection against reinfection for wild type virus from the SIREN study in the UK (1).

A preliminary analysis of reinfection trends in England suggested that the Delta variant may have a higher risk of reinfection compared to the Alpha variant (12); however, this analysis did not take into account the temporal trend in the population at risk for reinfection, which may have biased the findings.

Our findings are somewhat at odds with in vitro neutralization studies. Both the Beta and Delta variants are associated with decreased neutralization by some anti-receptor binding-domain (anti-RBD) and anti-N-terminal domain (anti-NTD) monoclonal antibodies though both Beta and Delta each remain responsive to at least one anti-RBD (4,5,13). In addition, Beta and Delta are relatively poorly neutralized by convalescent sera obtained from unvaccinated individuals infected with non-VOC virus (3–5,13). Lastly sera obtained from individuals after both one and two doses of the BNT162b2 (Pfizer) or ChAdOx1
(AstraZeneca) vaccines displayed lower neutralization of the Beta and Delta variants when compared to non-VOC and Alpha variant (5); although this does not have direct bearing on reinfection risk it is an important consideration for evaluating immune escape more broadly. Non-neutralizing antibodies and T-cell responses could explain the apparent disjuncture between our findings and the \textit{in vitro} immune escape demonstrated by both Beta and Delta.

\textbf{Strengths of this study}

Our study has two major strengths. Firstly, we analyzed a large routine national data set comprising all confirmed cases in the country, allowing a comprehensive analysis of suspected reinfections in the country. Secondly, we found consistent results using two different analytical methods, both of which accounted for the changing force of infection and increasing numbers of individuals at risk for reinfection.

\textbf{Limitations of this study}

The primary limitation of this study is that changes in testing practices, health-seeking behavior, or access to care have not been accounted for in these analyses. Estimates based on serological data from blood donors suggests substantial geographic variability in detection rates (14), which may contribute to the observed differences in reinfection patterns by province. Detection rates likely also vary through time and by other factors affecting access to testing, which may include occupation, age, and socioeconomic status. In particular, rapid antigen tests, which were introduced in South Africa in late 2020, may be under-reported despite mandatory reporting requirements. If under-reporting of antigen tests was substantial and time-varying it could influence our findings. However, comparing temporal trends in infection risk among those eligible for reinfection with the rest of the population, as in approach 2, mitigates against potential failure to detect a substantial increase in risk.

Reinfections were not confirmed by sequencing or by requiring a negative test between putative infections. Nevertheless, the 90-day window period between consecutive
positive tests reduces the possibility that suspected reinfections were predominantly the result of prolonged viral shedding. Furthermore, due to data limitations, we were unable to examine whether symptoms and severity in primary episodes correlate with protection against subsequent reinfection.

Lastly, while vaccination may increase protection in previously infected individuals (15–18), vaccination coverage in South Africa was very low during the time of the study (e.g., <3% of the population was fully vaccinated by 30 June 2021 (19)). Vaccination is therefore unlikely to have substantially influenced our findings. Increased vaccination uptake may reduce the risks of both primary infection and reinfection moving forward and would be an important consideration for application of our approach to other locations with higher vaccine coverage.

**Conclusion**

To date, we find no evidence that reinfection risk is higher as a result of the emergence of Beta or Delta variants of concern, suggesting the selective advantage that allowed these variants to spread derived primarily from increased transmissibility, rather than immune escape. The discrepancy between the population-level evidence presented here and expectations based on laboratory-based neutralization assays highlights the need to identify better correlates of immunity for assessing immune escape *in vitro*.

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Ethics statements

Ethical approval

Ethical approval: This study has received ethical clearance from University of the Witwatersrand (Clearance certificate number M160667) and approval under reciprocal review from Stellenbosch University (Project ID 19330, Ethics Reference Number N20/11/074_RECP_WITS_M160667_COVID-19).

Data availability statement

Data and code are available at https://github.com/jrcpulliam/reinfections. The following data are included in the repository:

- Counts of reinfections and primary infections by province, age group (5-year bands), and sex (M, F, U)
- Daily time series of primary infections and suspected reinfections by specimen receipt date (national)
- Model output: posterior samples from the MCMC fitting procedure and simulation results

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**Footnotes**

**Author contributions**

- **Conceptualization** - JP, CvS, JD, HM
- **Data collection, management, and validation** - NG, KM, AvG, CC
- **Data analysis** - JP, CvS, JD
- **Interpretation** - JP, AvG, CC, MJG, JD, HM
- **Drafting the manuscript** - JP
- **Manuscript review, revision, and approval** - all authors

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Competing interests

All authors have completed the ICMJE uniform disclosure form. CC and AvG have received funding from Sanofi Pasteur in the past 36 months. JRCP and KM serve on the Ministerial Advisory Committee on COVID-19 of the South African National Department of Health. The authors have declared no other relationships or activities that could appear to have influenced the submitted work.
## Supplementary Material

### Distribution of suspected reinfections by province, South Africa, March 2020 to June 2021

| Province                | No reinfection | One reinfection | Two reinfections | Total    |
|-------------------------|----------------|-----------------|------------------|----------|
| EASTERN CAPE            | 194,255        | 1,224           | 2                | 195,481  |
| FREE STATE              | 82,769         | 842             | 3                | 83,614   |
| GAUTENG                 | 409,419        | 5,832           | 40               | 415,291  |
| KWAZULU-NATAL           | 332,074        | 2,437           | 11               | 334,522  |
| LIMPOPO                 | 62,800         | 503             | 1                | 63,304   |
| MPUMALANGA              | 74,744         | 746             | 4                | 75,494   |
| NORTH WEST              | 63,200         | 892             | 7                | 64,099   |
| NORTHERN CAPE           | 36,126         | 413             | 1                | 36,540   |
| WESTERN CAPE            | 280,237        | 3,060           | 11               | 283,308  |
| UNKNOWN                 | 2              | 0               | 0                | 2        |
| **Total**               | **1,535,626**  | **15,949**      | **80**           | **1,551,655** |

### Breakdown of suspected reinfections by sex and age group (years), South Africa, March 2020 to June 2021

| Sex | Age group | No reinfection | One reinfection | Two reinfections | Total |
|-----|-----------|----------------|-----------------|------------------|-------|
| F   | (0,20]    | 84,241         | 506             | 3                | 84,750|
| F   | (20,40]   | 359,483        | 4,776           | 27               | 364,286|
| F   | (40,60]   | 303,546        | 3,366           | 8                | 306,920|
| F   | (60,80]   | 104,507        | 620             | 6                | 105,133|
| F   | (80,Inf]  | 16,486         | 101             | 0                | 16,587|
| M   | (0,20]    | 67,956         | 369             | 2                | 68,327|
| M   | (20,40]   | 247,359        | 3,039           | 15               | 250,413|
| M   | (40,60]   | 230,546        | 2,496           | 17               | 233,059|
| M   | (60,80]   | 79,777         | 588             | 2                | 80,367|
| M   | (80,Inf]  | 8,157          | 45              | 0                | 8,202 |
| **Total** | **1,502,058** | **15,906** | **80** | **1,518,044** |
Individuals with multiple suspected reinfections

Figure S1. Timing of infections for individuals with multiple suspected reinfections. Circles represent the first positive test of the first detected infection; triangles represent the first positive test of the suspected second infection; squares represent the first positive test of the suspected third infection. Colored bands represent wave periods, defined as the period for which the 7-day moving average of cases was at least 15% of the corresponding wave peak (purple = wave 1, pink = wave 2, orange = wave 3).
Timing of primary infections and reinfections by province

Figure S2. Number of detected primary infections (black) and suspected reinfections (blue), by province. Lines represent 7-day moving averages. The y-axis is shown on a log scale.
Province-level comparison of data to projections from the null model

Figure S3. Observed and expected temporal trends in reinfection numbers, for provinces with sufficient numbers of suspected reinfections. Blue lines (points) represent the 7-day moving average (daily values) of suspected reinfections. Grey lines (bands) represent mean predictions (95% projection intervals) from the null model. A and B: Gauteng. C and D: KwaZulu-Natal. E and F: Western Cape.
Approach 1: Convergence diagnostics

**Figure S4.** Convergence diagnostics and density of the posterior distribution for MCMC fits. A and B: MCMC chains for each parameter. C: Gelman-Rubin values (a.k.a. potential scale reduction factors) for each parameter; values less than 1.1 indicate sufficient mixing of chains to suggest convergence. D, G, I: posterior density for each parameter and the log likelihood. E, F, H: 2-D density plots showing correlations between parameters and the log likelihood.
Approach 2: Sensitivity analysis

Figure S5. Sensitivity analysis of empirical hazard ratio estimates to assumed observation probabilities for primary infections and reinfections. Estimates are shown for the full range of probabilities for which the overall mean relative hazard is between 0 and 1. The white polygon encloses the most plausible estimates (i.e. consistent with relative reinfection risk observed in the SIREN study (1) and observation probabilities for primary infection consistent with estimates based on seroprevalence data (14)). Top: Mean relative empirical hazard for reinfections versus primary infections in each wave, as a function of assumed observation probabilities for primary infections ($p_{\text{obs}_p}$) and reinfections ($p_{\text{obs}_r}$). A: wave 1, B: wave 2, C: wave 3. Bottom: Percent change in the mean relative empirical hazard for reinfections versus primary infections in waves 2 (D) and 3 (E) relative to wave 1, as a function of assumed observation probabilities for primary infections ($p_{\text{obs}_p}$) and reinfections ($p_{\text{obs}_r}$).