Appendix for:
Estimates of severity and transmissibility of novel South Africa SARS-CoV-2 variant 501Y.V2

Summary of epidemiology

Figure 1A summarises the epidemiology of COVID-19 in South Africa. After an initial steep rise in cases, South African authorities implemented a series of measures in mid to late March, including school closure on the 18th March and a national stay-home order as well as other stringent measures on 27th March, later referred to as alert level 5. This alert level persisted until the end of April, followed by level 4 through the end of May, level 3 through 15 August, and level 2 through 21 September. South Africa maintained level 1 from September through December, until resuming level 3 on 29 December in the attempt to control a clear second wave.

Cases and deaths initially peaked in July (mid winter) despite the easing of restrictions, suggesting that herd immunity had been achieved. Serological surveys (1) in sentinel populations (people living with HIV and pregnant women attending antenatal clinics) in the Cape Town Metropolitan area found seroprevalence of roughly 40% during the period 15 July through 7 August (1). This is consistent with our model projections for the 20-49 year old population during this period (Figure 1B; crosshairs indicate serosurvey results).

A resurgence of cases was first identified in the Eastern Cape in September, followed by the Western Cape and Kwa-Zulu Natal (2). This second wave has largely been attributed to the spread of the new variant 501Y.V2, which has rapidly become fixed as the dominant variant circulating in South Africa (Appendix Figure 1A).

South Africa transmission model

We used CovidM, an age-structured mathematical model of SARS-CoV-2 transmission which includes global estimates of populations and pathogen parameters (3–5) to consider a replacement variant of SARS-CoV-2 under different possible mechanisms. We used previously calculated posterior distributions of age-specific susceptibility and clinical fraction (4), demographic information for South Africa, previously estimated synthetic contact matrices (6), and model transmission in the urban population only, thus assuming that transmission and reporting are predominantly in this group (7). We calibrated the model using average R_t estimates from the EpiNow2 framework (8) applied to South African reported cases, corresponding to four different intervention eras: pre-intervention, post initial intervention, a relaxation period, and finally a variant dominated period (Appendix Figure 1B, Appendix Table 1).

For sample values from the susceptibility and clinical fraction posteriors as well as R_t estimates, we consider each parameter set with a series of steps:

1. Compute a population R_0 given susceptibility and clinical fraction, with the next-generation matrix method
2. Determine the scaling factor to match that R_0 to the pre-intervention R_t
3. Using simulated annealing, fit three reduction factors (one for school contacts, one for work and other contacts, and one for symptomatic transmission) that cause the

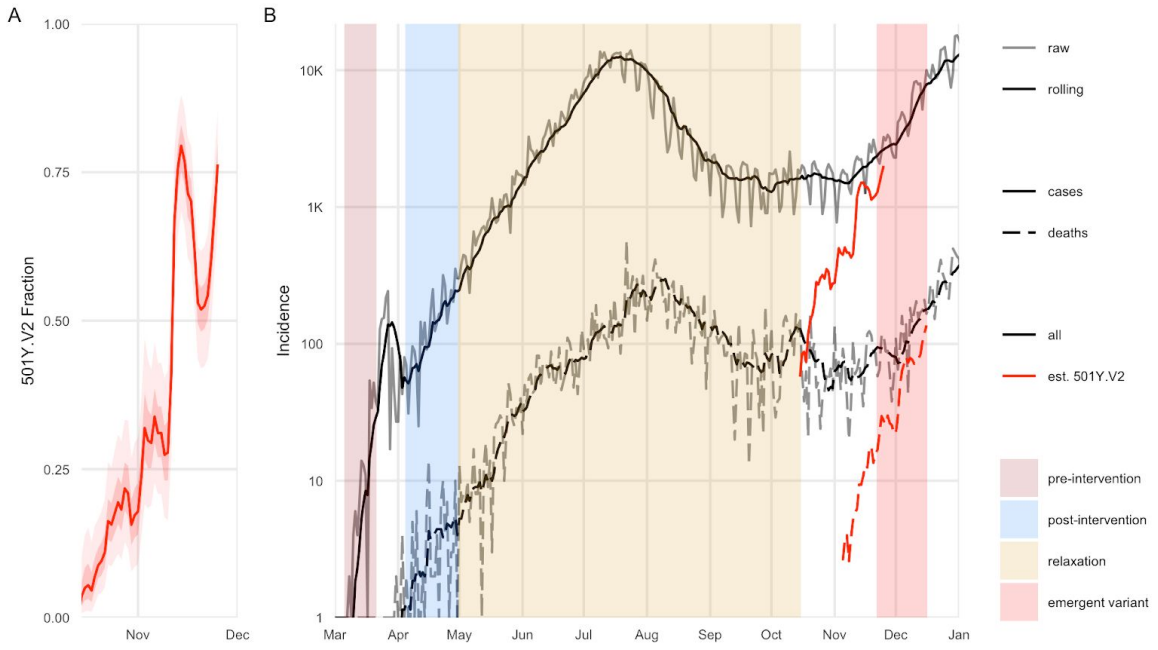
pre-intervention R_t to become the post-intervention R_t, again using next generation matrix method

4. Using simulated annealing to match reported cases in September, fit an ascertainment rate and a single relaxation curve that follows a logistic for those reduction parameters
5. Compute the projected attack rate through November 22; this corresponds to when sequencing prevalence has begun to saturate.
6. Use the attack rate and other population parameters to compute Reff and compare to the variant under different assumptions to determine the necessary increase in transmissibility or evasion of past-exposure immunity, again using next generation matrix method

The resulting fitting estimates are captured in Appendix Table 1.

Parameter	**Median (95% CrI)**
School contact reduction	82% (67-88)
Work, Other reduction	58% (38-70)
Symptomatic transmission reduction	42% (11-70)
Intervention Logistic Decay Rate	0.04 (0.01-0.15)
Intervention Decay Midpoint	26 Aug (14 Aug - 18 Sep)
Symptomatic Case Ascertainment	3% (1-24)

Appendix Table 1: Model Intervention Parameter Estimates.



Appendix Figure 1: Prevalence of 501Y.V2 and Fitting Periods for Model.
A: fraction of sequenced cases in South Africa of the 501Y.V2 variant. B: epidemiological trends in South Africa for reported cases and deaths and associated model fitting eras (shaded regions).

Era	Start, end (2020)	Median static R_t (50% credible interval)
pre-intervention	Mar 6 to 21	3.22 (2.85, 3.61)
post-intervention	Mar 29 to Apr 28	1.40 (1.30, 1.50)
relaxation	Aug 31 to Oct 15	-- (time varying)
emergent variant	Nov 22 to Dec 09	1.34 (1.31, 1.38)

Appendix Table 2: R_t values by era.
Start and end dates denote fitting intervals; pre-intervention values apply to all time prior to the window, post-intervention between pre- and relaxation window, and relaxation window until the emergent variant. We selected the start of the window for the emergent variant corresponding to when we judge reported cases are practically all of the new variant, so that the growth estimate does not represent a mixture of different variants.

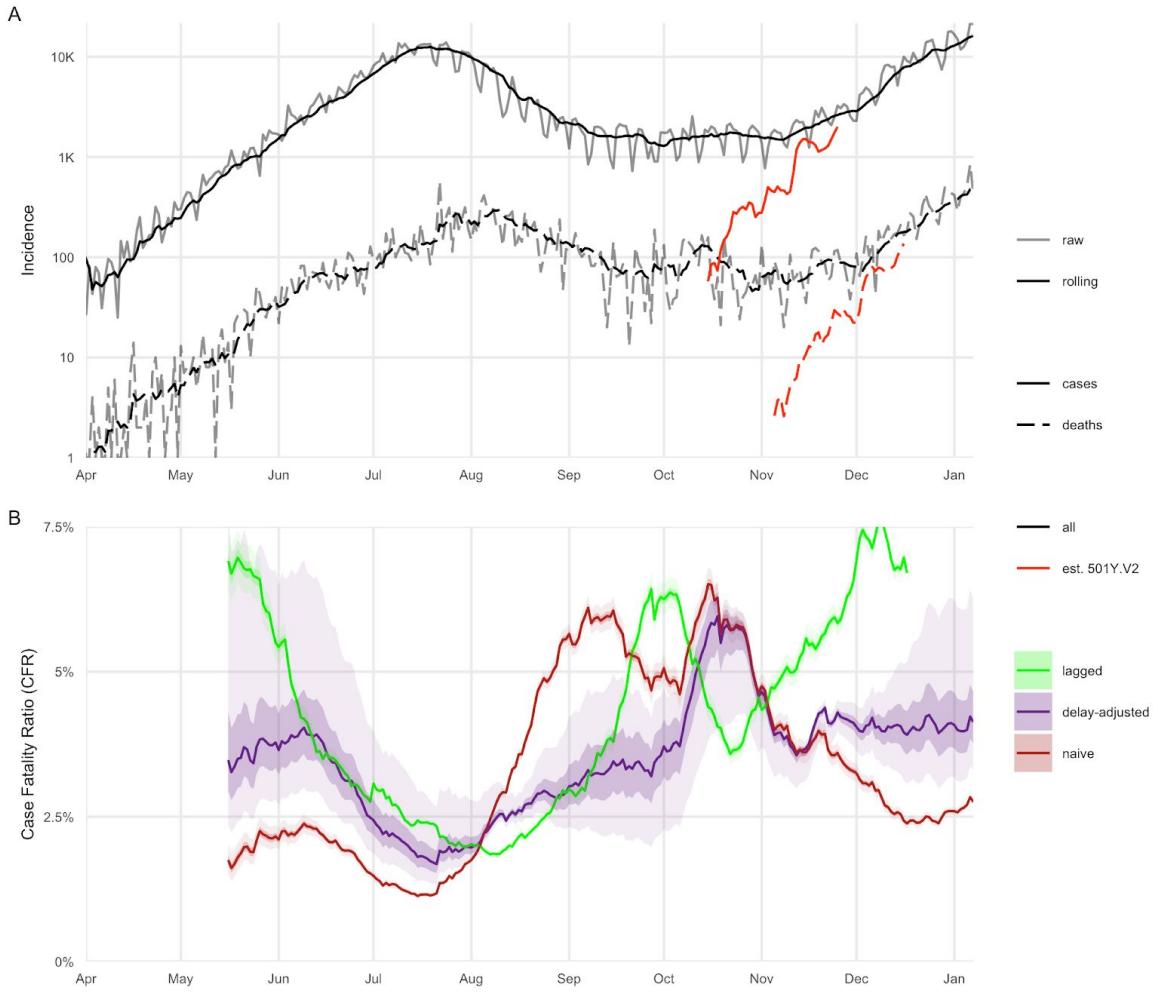
Estimating the case fatality ratio (CFR) through time

We followed the methods of Nishiura et al. (2009) (9) to adjust the confirmed case time series in South Africa for right-censoring, i.e. the delay between case confirmation and death (9,10). On the time-scale of days, we convolve the case time-series with the cumulative probability distribution representing the time between hospitalisation-to-death reported in Linton et al. (2020) (11) to estimate the new number cases each day with “known outcomes”, i.e. estimating the number of cases that would have seen the resolution of their case as either recovery or death. We use the cumulative distribution function of the reported Log-normal distribution adjusted for right-truncation, with a mean of 13 days (95% confidence interval: 8.7—20.9) and a standard deviation of 12.7 days (95% CI: 6.4—26.0) for the convolution with the case time-series.

We compute the uncertainty around the time-varying delay-adjusted CFR (dCFR) estimate by assuming the reported uncertainty range for both the reported mean and standard deviation are normally distributed. We then bootstrap over both distributions, computing the convolution for each sampled pair of parameters. We run this bootstrap for 100,000 iterations and compute the 95% quantiles over all iterations for the final 95% range (Appendix Figure 1, panel A). To test the robustness of the assumption within the bootstrapping calculation — that the reported parameters were normally distributed — we performed the same calculation assuming a uniform distribution, with minimum and maximum values taken directly from the minimum and maximum of the reported ranges and found that the resulting uncertainty range of the time-varying dCFR was indistinguishable, suggesting the parameter space is well-covered using either approach along with high numbers of iterations.

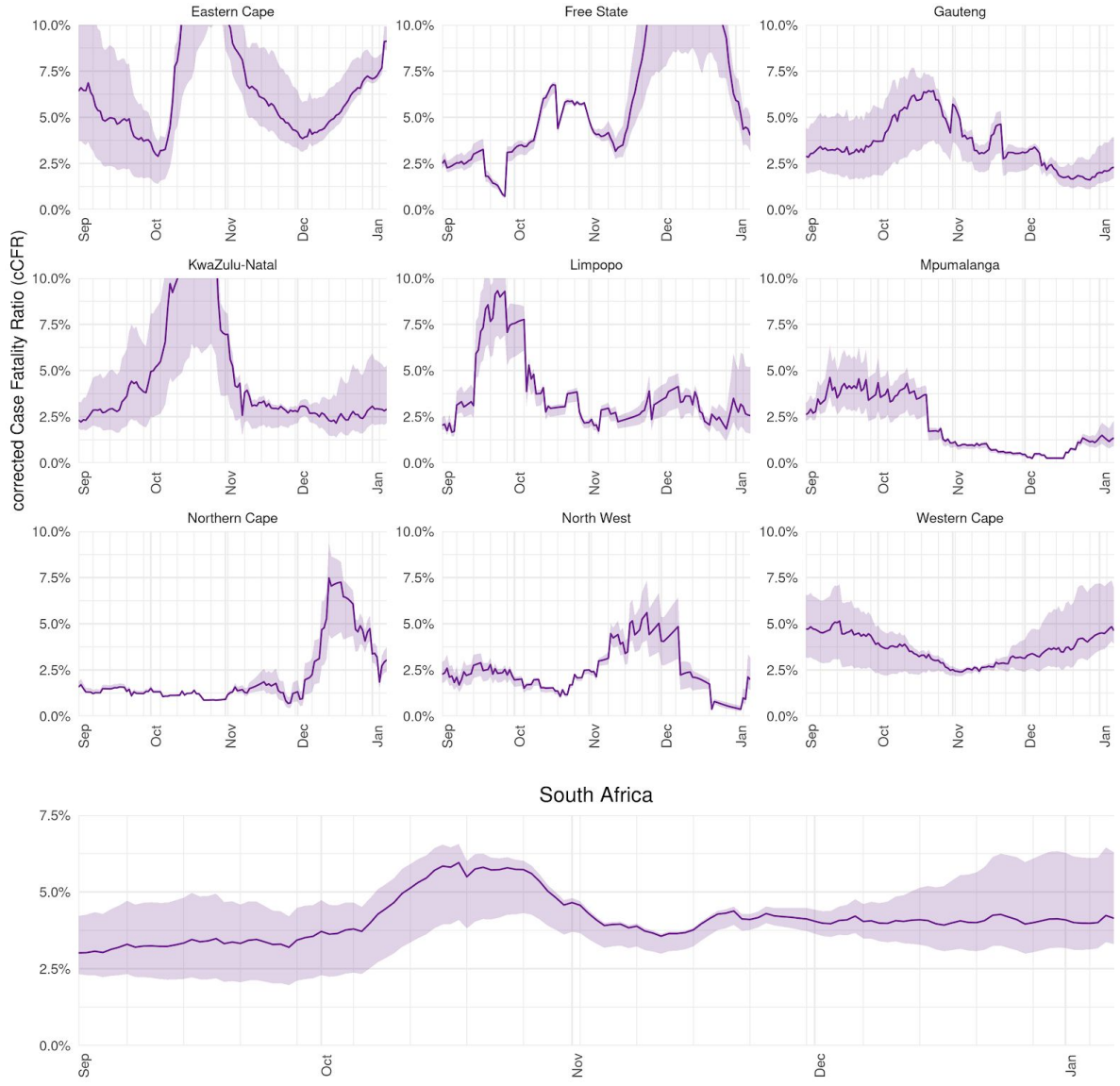
The confirmed case time-series is subject to possible under-ascertainment of infections. However, we are interested in any relative change in the dCFR over-time. Specifically, we are interested in whether the CFR has increased recently, given that the new strain has been circulating in South Africa for long enough for changes in severity to be detected — once the delay between confirmation-to-death is adjusted for.

Appendix Figure 2 shows the estimates of the time-varying CFR using different methods along with raw data on cases and deaths; the naïve (crude ratio by day, nCFR) and lagged (deaths offset by a fixed interval, lCFR) methods are shown to highlight how widely they diverge from the preferred dCFR. Based on the nationally aggregated data, we did not find any increasing dCFR (Appendix Figure 2B), but when we considered provinces separately (Appendix Figure 3) we found evidence that the delay-adjusted CFR has increased in most provinces since arrival of the new variant, and particularly in the the Western Cape province which has the most reliable data based on excess death time-series (12).



Appendix Figure 2: Summary of the change in severity due to the new strain in South Africa. A: New confirmed COVID-19 cases and deaths in South Africa; rolling window is 7 day average. B: Using those confirmed outcomes, the time-series of the case fatality ratio, using different analytical approaches.

Note, however, that there have been large changes in the estimated dCFR over time (Appendix Figure 3). A decline in dCFR following the peak in cases would be expected if the delays from cases to deaths were longer than is being assumed here. If this is the case and we are not properly accounting for these delays, then the increase in CFR might be greater than is estimated here.



Appendix Figure 3: Summary of the change in severity due to the new strain in South Africa. dCFR for each of the provinces and for all of South Africa (bottom row) for between-province comparison. We use the Western Cape province in the main text as the high correlation between the excess death time-series and the time-series of deaths attributed to COVID-19 indicates levels of reporting are highest and most consistent in this region.

Code Availability

Simulation and analysis code is available from https://github.com/cmmid/SA2UK.

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