# Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

**SUPPLEMENTARY INFORMATION**

# Challenges in inferring intrinsic severity of SARS-CoV-2 Omicron variant

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## SUPPLEMENTARY TEXT

### Reinfections and post-vaccine infections are more common with Omicron than previous variants

Omicron has clearly shown more ability than Delta to cause infection in individuals with pre-existing immunity from either prior infection or vaccination. This was first observed in South Africa, where even after correcting for an increase in baseline population immunity, reinfections were noted to occur at a faster rate than prior waves[1]. Since then, multiple studies have corroborated the finding that Omicron is far more likely than Delta to infect those with documented prior infection or prior vaccination[2-4], consistent with its partial escape from *in vitro* neutralization by serum from previously infected or vaccinated individuals[5]. Indeed, early vaccine effectiveness analysis from the Health Security Agency used a test-negative case-control analysis to estimate Omicron-specific effectiveness of unboosted vaccines at less than 40% by 3 months after the primary series, considerably lower than against Delta or any prior variant, though boosters helped somewhat, and effectiveness against hospitalization was relatively preserved[6].

### Estimates of seroprevalence and immune evasion of Omicron

The conceptual schematic in the **Diagram** depicts vaccine efficacy estimates of 80% for Delta[7,8] and 25% for Omicron[9], and seroprevalence taken from a midpoint of estimates from serosurveys performed in several different South African settings prior to the Delta wave[10,11], conservatively assuming half of the remaining susceptible population attained immunity from Delta or vaccines prior to the arrival of Omicron. South African epidemic curves[12] and cumulative vaccination statistics[13] shown above were collated by Our World In Data; underlying data for the epidemic curves were compiled by the COVID-19 Data Repository by the Center for Systems Science and Engineering at Johns Hopkins University[14].

**Early assessments of comparative population-level impact of Omicron, and implications for intrinsic severity**

Several studies have already begun to assess the initial impact of Omicron compared with prior variants, typically Delta, on hospitalizations, ICU admissions, mechanical ventilation, and death related to COVID-19[2-4,15-18]. Early studies of such a rapidly-spreading epidemic in which severity manifests late in the disease course must carefully ensure that cases are followed through to completion of illness and compared with an appropriately lagged denominator of total cases in order for fair comparison with prior waves, or even contemporaneously circulating variants that are declining in incidence. Despite these challenges, such systematic studies are essential in estimating the impact of the rapidly-spreading Omicron variant.

Early indications from South Africa[15,18], the United Kingdom[3], Canada[17], and the United States[2,4,16] all indicate lower per-case hospitalizations, and those that have been powered to look also show reduced per-case rates of ICU admissions and death compared with the Delta variant. In South Africa, where Omicron was first discovered and has been circulating the longest, cases peaked in mid-December 2021 at 117% of their prior peak (during the Delta wave)[12], whereas COVID-19 hospitalizations peaked at 56% of their prior peak (during the earlier Beta wave; they reached 64% of their peak during the Delta wave)[19], and excess deaths from any cause, which had returned to near-baseline levels after the conclusion of the Delta wave, are around 30% greater than expected as of this writing, compared with ~100% greater during the Delta surge and ~150% greater during the Beta surge[20]. Crude, unadjusted analyses from other countries appear to corroborate these trends to varying degrees, albeit with some variability that may relate to population age and immunity, especially among those infected in the earliest Omicron waves in each locale.

However, these aggregate outcome measures conflate properties of the virus itself with properties of the population it infects; severity reflects an interplay between virus and host. Critically, in addition to virulence intrinsic to the variant itself, these measures of severity will encompass protection derived from immunity, as well as the increased ability of Omicron to infect individuals with immunity (derived from either infection or vaccination), who are more numerous now than in prior waves. While some studies report overall measures of severity compared with prior waves[2] or contemporaneous Delta cases, most adjust for and/or stratify by age and vaccination status[16,17], while others also account for known prior infections[4,15]. However, the majority of past infections are undiagnosed, to different degrees in different settings. Only two studies attempted to correct for these patients with undocumented prior infection[3,18], which would be expected to confer immunity in the unvaccinated or improved "hybrid immunity" in those also vaccinated, as seen with documented infections[3,5]. As expected, the average severity of Omicron cases relative to Delta was lowest in the crude (unadjusted) comparisons, showing roughly three to five-fold reductions in risk of hospital admission per case[2,15]. Adjusting for age and vaccination status increased the apparent severity of Omicron relative to Delta, with overall adjusted hazard ratios for hospitalization rising to around 0.3-0.5[4,15,16]. Two studies modeled undetected infections, each assuming that the roughly five- to ten-fold increased propensity of Omicron compared with Delta to reinfect individuals would remain constant whether their prior infection was known or unknown. Each study, one from the UK[3] and one from South Africa[18], estimated the fraction of infections that had been missed in their locale. Despite drastically different rates of documented prior infection in each region, with this adjustment, each of these two models estimated that Omicron was roughly 75% as likely as Delta to cause hospitalization in naïve hosts[3,18]. Of note, Delta was approximately twice as likely to lead to hospitalization as Alpha[21-23], implying that in non-immune hosts, Omicron may be roughly as likely to lead to hospitalization as Alpha. In individuals vaccinated with two doses of mRNA vaccines, multiple studies indicated that Omicron and Delta were equivalently likely to

lead to hospitalizations[3,4]. Early indications in some[4,16,17] but not all[15] of these studies suggest that hospitalizations may be less severe on average for Omicron cases, though this is not yet clearly broken down by vaccination or prior infection status; further analyses are needed to determine how much of this is related to the variant itself, versus the immunity of the hosts infected by it. In addition to adjustments for age, vaccination status, and prior infection (known or unknown), ensuring sufficient time for more serious outcomes to develop will be critical in systematically assessing this issue, which is challenging at the moment given the very recent rise to dominance of Omicron.

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