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### **Challenges in inferring intrinsic severity of SARS-CoV-2 Omicron variant from early population-level impact**

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## **Abstract**

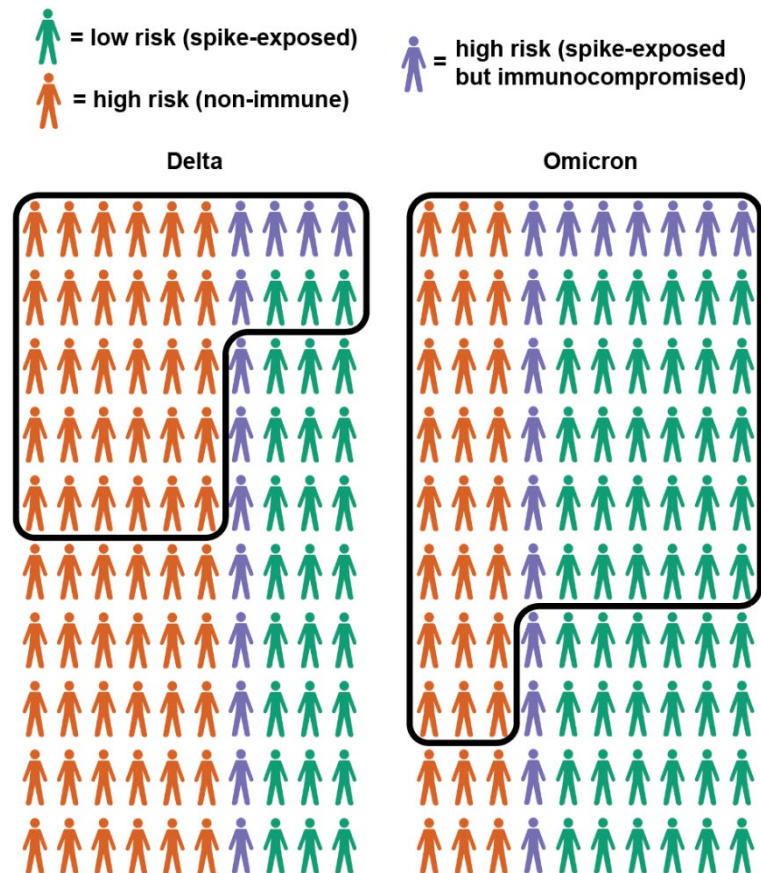
Inferring the severity of an emerging infectious agent presents specific challenges due to the inevitably imperfect state of data early in an epidemic. Here we specifically consider the additional impact of existing population immunity on estimates of intrinsic virulence, using the example of early evidence of the Omicron variant of SARS-CoV-2 emerging in South Africa. Without accounting for vaccination rates and prior infections, among other factors, the true risk of severe infection will be systematically underestimated. At the time of writing it is premature to consider Omicron infections to be intrinsically milder than those caused by preceding variants.

Active genomic surveillance and transparent communication by South African scientists and public health practitioners recently heralded a novel, rapidly circulating SARS-CoV-2 variant that has come to be called Omicron. Since then, scientists and the public alike are watching closely to see the clinical impacts of the Omicron wave that has swept rapidly through the population, in order to estimate the relative transmissibility, immune evasion, and severity compared with prior variants. The growth advantage of Omicron over Delta, now replicated in multiple locales, is already clear. As early indications are that the extraordinarily rapid spread of Omicron through South Africa has led to fewer hospitalizations and deaths than were seen in similar stages of prior waves, some members of a weary public are understandably eager to ascribe that observation to lower intrinsic virulence of this variant. However, even more than with prior variants, caution is warranted in inferring intrinsic traits of Omicron from population-level observations, particularly for severity.

One key difference in interpreting the population-level severity of Omicron is the level of immunity in the affected populations. After three prior waves, dominated by D614G, then Beta, and most recently Delta, by mid-November South Africa had achieved their lowest recorded daily cases since the earliest days of the pandemic. While this brief period of control was certainly multifactorial, a key contributor is expected to be the accumulated immunity from prior waves, as well as a vaccination program that began ramping up in mid-2021, during the winter months in the southern hemisphere, prioritizing the elderly first. Much of this population immunity was new since the most recent wave caused by Delta, both since that wave infected the most people, and because vaccines were distributed concurrently with that wave. Thus, Omicron enters a South African population with considerably more immunity than any prior SARS-CoV-2 variant has encountered, enriched among those who would have been at greatest risk for severe outcomes.

Further, Omicron is better at infecting those with prior immunity than any preceding variant. Reinfections have occurred at a faster rate in South Africa than in prior waves, even accounting for the increase in baseline population immunity<sup>6</sup>. Early *in vitro* data from live virus demonstrate reduced neutralization by convalescent or vaccinated sera by up to 40-fold<sup>7,8</sup>, as well as by some therapeutic monoclonal antibodies<sup>8,9</sup>. And in the early days of Omicron spread in the UK, the Health Security Agency estimates Omicron-specific efficacy of the AstraZeneca vaccine at 0% and of the Pfizer/BioNTech vaccine at 30%, considerably lower than against any prior variant<sup>3</sup>.

Thus, a greater fraction of individuals infected by Omicron will have pre-existing immunity than with any prior variant, both because more of the population has immunity, and because Omicron is better equipped to infect those immune individuals. This alone complicates comparisons of population-level infection-fatality rate (IFR) compared with prior waves (Figure 1), since people with pre-existing immunity are expected to have less severe outcomes from subsequent infection. Furthermore, a productive infection in hosts with prior immunity likely results from properties of both the virus and the host. When such infections are caused by less intrinsically immune-evasive variants, the previously immune hosts who do end up infected may be enriched for



**Figure 1. Challenges in comparing IFR of Omicron vs Delta variants.** Differences in population-level immunity and propensity to infect individuals with prior immunity confound direct comparisons of IFR between the Delta and Omicron variants. Delta (left) swept South Africa in June-August 2021, when population immunity was lower. By contrast, Omicron (right) encountered a population with fewer non-immune individuals (orange), and can more readily infect immune individuals (green). Figure depicts vaccine efficacy estimates of 60% for Delta (78% in immunocompetent hosts)<sup>1,2</sup> and 25% for Omicron (31% in immunocompetent hosts)<sup>3</sup>, and seroprevalence taken from a midpoint of estimates from serosurveys prior to the Delta wave<sup>4,5</sup>, and conservatively assuming half of the remaining susceptible population reached immunity from Delta or vaccines. Thus, Omicron is expected to infect many more individuals at low risk for severe outcomes due to prior immunity, which will artifactually reduce observed IFR.

those with less effective immune responses, either because of immune defects or less robust responses to either vaccine or past infection. Such individuals with less robust immune protection against infection are likely also more susceptible on average to worse outcomes from these infections. By contrast, when the propensity to evade immunity is driven more by viral properties, the selection for susceptible spike-exposed hosts required for infection will be less, meaning that more hosts with robust immune responses will be infected – and may tolerate these infections with less severe consequences. Each of these factors would tend to drive observed IFR, and perhaps even IFR in breakthrough infections, lower than for prior variants, even if Omicron itself has the same intrinsic severity.

Even beyond this, other challenges remain in extrapolating observed IFR in South Africa to other locales, including its relatively young overall age distribution, idiosyncrasies of social networks driving initial spread, and changes in case ascertainment relative to prior waves given the increased visibility of Omicron. When comparing hospitalizations or deaths between variants with different transmissibility, it is also essential to account for the lag in time between infection and these more severe outcomes, as a naïve comparison will artificially inflate the severity of the less transmissible variant even assuming the lag is identical, because the total number of recorded cases of a more transmissible variant will be greater during that lag period – increasing the denominator of total cases.

The best way to distill intrinsic severity of Omicron relative to other variants would be a contemporaneous comparison with a co-circulating variant. However, Omicron's dramatically rapid rise to dominance at a time of low Delta incidence has made such comparisons impossible in South Africa. Indeed, even in areas with ongoing Delta spread such as the UK, Omicron is quickly rising in frequency, and time will tell if Delta will co-circulate, or if Omicron will sweep Delta aside. Even if there is an appreciable period of co-circulation, the baseline immunity of patients infected by one variant or the other may systematically differ. Thus, carefully controlled comparisons, whether contemporaneous or historical, will be required to assess the relative intrinsic severity of the variants themselves, independent of circumstance or pre-existing immunity.

Such measurements of intrinsic severity are critical for anticipating the impact of Omicron on societies with differing amounts and distributions of population immunity, which will vary in terms of the vaccines used, people immunized, and existing immunity from prior infection. Extrapolating population-level impact from one setting to another requires extreme caution: non-immune individuals will not be spared by a variant whose lower IFR is driven by its capacity to infect hosts with prior immunity; on the contrary, non-immune individuals would be at greater risk in that scenario, since they would be more likely to encounter such a virus, which may be of equivalent severity. And at the population level, with such rapid spread, these adverse encounters would happen on an even more compressed timescale, exacerbating overcrowding of hospital systems and caregivers already stretched to the brink by an ongoing pandemic.

Viruses have no intrinsic tendency to evolve towards lower virulence; evolution simply selects those that excel at making more of themselves. In an illness like COVID-19 where the vast majority of spread occurs prior to severe disease, severity is likely not directly selected upon at all. HIV is a classic example of a successful pathogen despite being fatal in >99% of cases if untreated. Indeed, previously observed variants of SARS-CoV-2 with enhanced transmission (Alpha and Delta) appear to have greater intrinsic severity<sup>10-13</sup>. While the lower observed IFR in the early weeks of the Omicron wave in South Africa is better than the alternative, the most likely explanation lies in increased immunity among those being infected; more time and careful comparisons controlling for age, prior immunity, detection bias, lag period, hospital capacity, and numerous other factors will be required to infer anything about intrinsic virulence. Our collective intuition on how population-level IFR relates to intrinsic severity of a variant needs to be recalibrated over time as immunity accrues, and far more so with a variant as immune-evasive as Omicron.

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