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Perspective

Challenges in Inferring Intrinsic Severity of the SARS-CoV-2 Omicron Variant

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Active genomic surveillance and transparent communication by South African scientists and public health practitioners recently heralded a new, rapidly circulating SARS-CoV-2 variant, now called omicron.[1] Scientists and the public have been closely monitoring the clinical effects of the omicron-variant wave that has rapidly swept through the population in order to estimate the variant's relative transmissibility, capability for immune evasion, and severity as compared with previous variants. Omicron's growth advantage over the delta variant has now been documented in multiple locations. Omicron's rapid spread throughout South Africa has resulted in fewer hospitalizations and deaths per documented case than were seen during previous Covid-19 waves, an observation that some members of a weary public are understandably eager to ascribe to an intrinsic tendency of this variant to cause less severe illness. Even more than for previous variants, however, caution is warranted when it comes to making inferences about omicron's intrinsic traits, particularly its severity, on the basis of population-level observations.

One important factor that should guide the interpretation of omicron's population-level severity is the level of immunity in affected populations. After three previous waves — dominated by the D614G, beta, and then delta variants — by mid-November 2021, South Africa reported its lowest daily case count since the earliest days of the pandemic. Although this brief period of control was certainly multifactorial, a key contributor is thought to have been the immunity acquired during previous waves (especially the delta-variant wave) and a vaccination program that began ramping up in mid-2021, which prioritized elderly people. Omicron therefore entered a South African population that had considerably more immunity than any previous SARS-CoV-2 variant had encountered, especially among people who would have been at greatest risk for severe outcomes. Omicron has also been shown to be far better than previous variants at infecting people who have some degree of preexisting immunity because of vaccination or a previous infection, although boosters reduce infection risk, and vaccines' effectiveness against hospitalization is largely preserved (see the Supplementary Appendix, available at NEJM.org).

As compared with people infected with previous variants, a higher proportion of people infected with omicron will therefore have preexisting immunity, both because more of the population

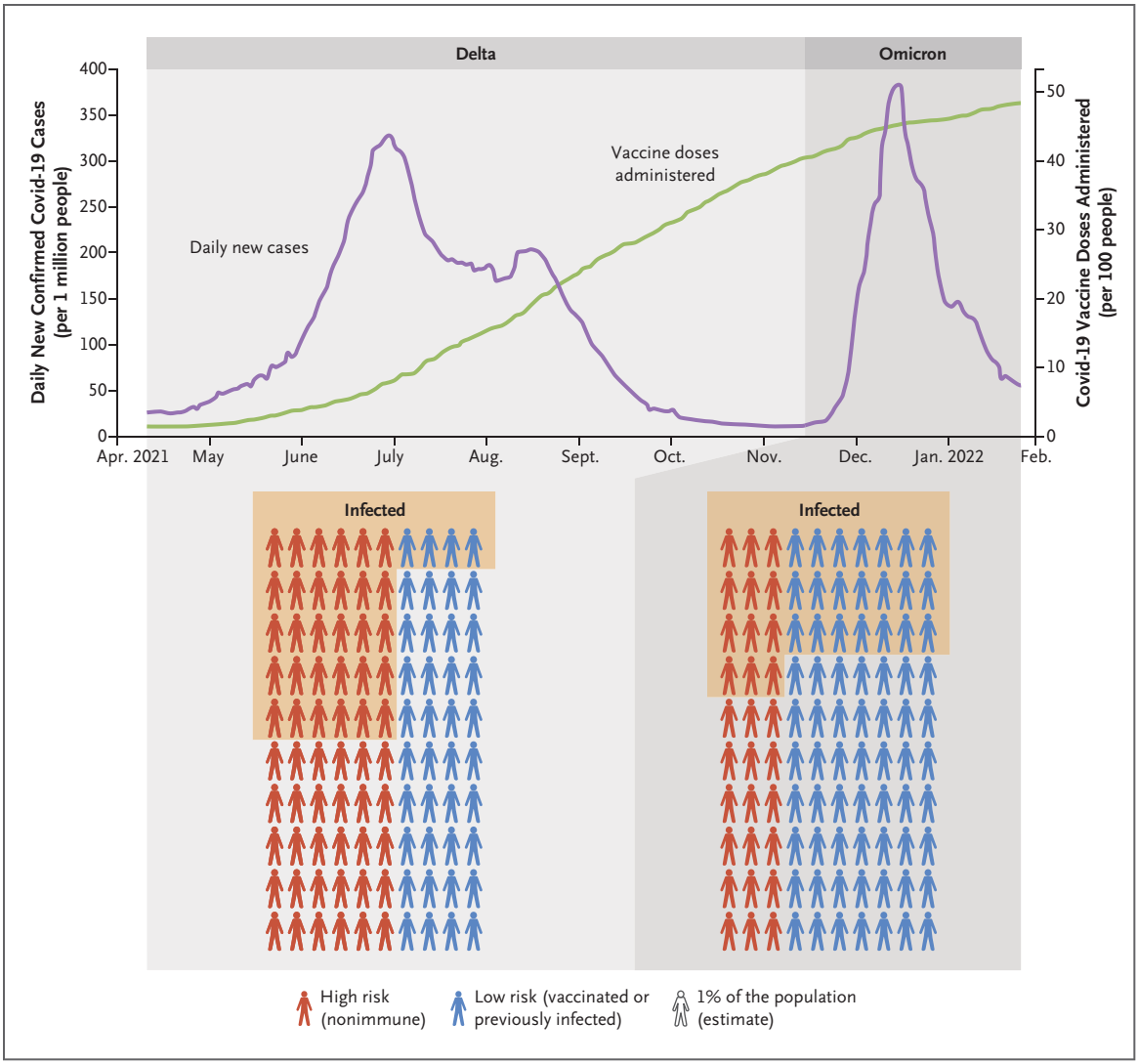
now has immunity and because omicron is better equipped to infect people with preexisting immunity. The case fatality rate (CFR) is an important measure of an infection's severity, but not all infections are recorded, and the proportion of cases that are detected may change over time. It's therefore important to distinguish between the CFR and the infection fatality rate (IFR), particularly since more serious infections are more likely to be recorded. The increase in population immunity complicates comparisons between omicron's population-level severity, whether measured by CFR or IFR, and that of previous variants (see diagram), since people with preexisting immunity are expected to have less severe outcomes from subsequent infection.

Furthermore, the likelihood of a person with preexisting immunity developing a productive infection, and the clinical characteristics of that infection, are probably a function of both viral and host properties. When such infections are caused by variants with less intrinsic immune-evasion capability, such as delta, the population with preexisting immunity that becomes infected is expected to include a disproportionate share of people with less effective immune responses, whether because of immunologic defects, a less robust response to vaccination or past infection, or the waning of a previously protective immune response. Some people with less robust protection against infection may also be at higher-than-average risk for poor outcomes from these infections, for example, owing to immunosenescence in older populations. By contrast, if a variant's immune-evasion capability is driven mainly by its own properties, including a divergent spike protein, more people with robust immune responses may be infected — and their infections may have less severe consequences. Each of these factors would tend to drive down the CFR, perhaps including the CFR for breakthrough infections, to a rate lower than that for previous variants, even if omicron has the same intrinsic propensity to cause severe disease.

There are other challenges associated with extrapolating the unadjusted CFR in South Africa to other locations, including the country's relatively young population; the nonrepresentative age, degree of immunity, and prevalence of coexisting conditions among the social networks that drove omicron's initial spread; and possible changes in case ascertainment from previous waves, owing to increased testing given omicron's global visibility. When comparing hospitalizations or deaths caused by variants with differing transmissibility, it's also essential to account for the lag time between infection and severe outcomes. Even if two variants have the same lag time, a comparison that doesn't take this lag into consideration will artificially inflate the less transmissible variant's apparent severity, since the total number of accrued cases of the more transmissible variant will be greater during this period — thereby increasing the denominator of total cases.

Several epidemiologic studies have compared the severity of early omicron cases with infections caused by previous variants, especially delta. Most of these studies have attempted to adjust for key differences in the infected populations that affect disease severity, notably age and degree of preexisting immunity owing to vaccination or previous infection. Although vaccination status is generally well documented, only a minority of cases globally are documented, and the rate of underascertainment varies considerably by place and time. Whereas crude estimates incorporating all reported cases suggest that omicron is far less severe than delta on average, omicron's estimated relative severity is greater in analyses that account for vaccination status and documented previous infection. This finding is in keeping with the likelihood that a portion of the observed reduction in severity stems from omicron's greater ability to infect people with preexisting immunity, which protects somewhat against severe disease. Only two studies have attempted to model the effects of undocumented previous infections to estimate omicron's intrinsic severity relative to delta. Although these studies were conducted in locations with very different case-ascertainment rates, after correcting for underascertainment, each study estimated that omicron was about 75% as likely as delta to cause hospitalization in an unvaccinated person with no history of SARS-CoV-2 infection.[2,3] This meaningful but fairly small difference implies that omicron, alpha, and wild-type SARS-CoV-2 have similar intrinsic severity.

Such intrinsic-severity estimates are critical for anticipating omicron's effects on societies with various levels and distributions of population immunity, which will be influenced by the type of vaccines used, the proportion of people immunized, and the rate of preexisting immunity owing to previous infection. Extrapolating population-level effects from one



Inferring Infection Fatality Rates for the Delta and Omicron Variants of SARS-CoV-2.

Differences in population-level immunity and propensity to infect people with preexisting immunity confound direct comparisons of the infection fatality rate between the delta and omicron variants of SARS-CoV-2. Data shown are from South Africa from April 12, 2021, to January 25, 2022. The delta variant (left) swept through South Africa from June through August 2021, when population immunity was lower. By contrast, the omicron variant (right), in November and December 2021, encountered a population with fewer nonimmune people (shown in red) because of both previous infection (including with the delta variant) and vaccination (line graph), and omicron can more readily infect people with preexisting immunity (shown in blue). Omicron is therefore expected to infect many more people who are at low risk for severe outcomes owing to preexisting immunity, which will reduce the observed infection fatality rate independently of the intrinsic severity of the variant. See the Supplementary Appendix for details of the vaccine efficacy and seroprevalence estimates depicted.

setting to another requires extreme caution: nonimmune people (including immunocompromised people) wouldn't be spared by a variant whose lower IFR is driven primarily by its capacity to infect people who have preexisting immunity. On the contrary, omicron's immune-evasion capability has enabled it to infect many people who wouldn't have been infected by previous variants, which has fueled its rapid spread and allowed it to more quickly infect nonimmune people, thereby offsetting what appears to be a moderately lower intrinsic severity and exacerbating overcrowding of hospital systems and demands on caregivers.

Viruses don't inevitably evolve toward being less virulent; evolution simply selects those that excel at multiplying. In the case of

Covid-19, in which the vast majority of transmission occurs before disease becomes severe, reduced severity may not be directly selected for at all. Indeed, previous SARS-CoV-2 variants with enhanced transmissibility (e.g., alpha and delta) appear to have greater intrinsic severity than their immediate ancestors or the previously dominant variant.[4,5] Although the reduced CFR seen in the early weeks of South Africa's omicron-variant wave is better than the alternative, much of the observed difference relates to increased immunity among the people being infected. More time and careful comparisons controlling for age, preexisting immunity, detection bias, lag time, hospital capacity, and other factors will be required to determine omicron's intrinsic virulence. Given the remarkable pace at which omicron has spread, its societal effects will probably be substantial, particularly considering an intrinsic severity that is higher than crude comparisons might suggest. Our collective intuition regarding how a population-level CFR or IFR relates to a variant's intrinsic severity needs to be recalibrated over time as immunity accrues — especially with a variant with the immune-evasion capabilities of omicron.

Disclosure forms provided by the authors are available at NEJM.org.

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