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Omicron — Decoupling Infection from Severe Disease

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South Africa, like much of Africa, suffers from relatively low Covid-19 vaccine coverage, with only 43% of South African adults having been fully vaccinated. However, immunity can result from either vaccination or previous infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), so vaccine coverage alone does not capture population immunity. South Africa has faced four waves of the Covid-19 pandemic, each dominated by a different variant of SARS-CoV-2,[1] which suggests the possibility of a high prevalence of underlying seropositivity due to previous infection. Seropositivity could affect the severity of disease caused by new variants.[2]

A report by Madhi et al. in this issue of the *Journal*[3] suggests that, in the Gauteng province of South Africa, a high level of previous SARS-CoV-2 infection may have contributed to a decoupling of infection from hospitalization and death during the most recent wave of Covid-19, as compared with the proportions seen in previous waves. In this carefully conducted seroepidemiologic study, the investigators estimated the population seroprevalence by testing dried-blood-spot samples, obtained from more than 7000 persons, for antibodies to SARS-CoV-2 spike and nucleocapsid proteins. The study was conducted after the first three waves of Covid-19 but before the fourth wave, which was dominated by the B.1.1.529 (omicron) variant. The study shows an overall population seroprevalence in Gauteng of 73.1%. The seroprevalence varied according to district (ranging from 66.7% in Tshwane to 76.2% in Johannesburg) and according to age (ranging from 56.2% among children <12 years of age to 79.7% among adults >50 years of age). In South Africa, Covid-19 vaccines are not yet approved for children younger than 12 years of age, so vaccination would not account for seropositivity in this group. Thus, more than half the children residing in Gauteng appear to have been previously infected with SARS-CoV-2.

Madhi et al. also found that the incidence of SARS-CoV-2 infection increased and subsequently declined more rapidly during the fourth wave of Covid-19 in South Africa than it had in previous waves. This change, along with the decoupling of the incidence of infection from the incidences of hospitalization and death due to Covid-19, suggests that the omicron variant had a reduced ability to cause severe disease in this population. It is important to note that when community infection is overwhelming, it can be difficult to distinguish hospital admissions due to SARS-CoV-2 from admissions in which SARS-CoV-2 is detected incidentally, particularly in health care systems that routinely conduct Covid-19 screening at the time of hospital admission.

These data from South Africa have global implications, now that the omicron variant accounts for more than 98% of reported SARS-CoV-2 sequences. The omicron variant, which was first detected in South Africa,[1] contains more than 30 mutations in the spike protein and is resistant to antibody neutralization.[4] Thus, vaccines have a reduced ability to prevent infection with this variant, but they still have efficacy against severe disease.[5] This protection against severe disease is consistent with the finding that CD4 and CD8 T-cell responses, which can be triggered by infection or vaccination, show resilience against the omicron variant.[6] It is tempting to associate the decoupling of infection from hos-

pitalization and death that occurred during the omicron-dominant wave in South Africa with the high level of population immunity at that time. However, these clinical outcomes may be specific to the omicron variant, which has mutations that may confer altered tropism and reduced disease severity.[7] Clinical outcomes may not be the same with a future SARS-CoV-2 variant, because there is no guarantee that such a variant would be derived from the omicron variant or share the reduced pathogenicity that may characterize this variant.

Although this study shows a high prevalence of seropositivity, studies of seroprevalence may underestimate true population exposure. The investigators measured antibody responses, which wane relatively quickly. The study may not have captured infections that had occurred many months earlier, particularly mild infections, which trigger lower levels of antibodies. In addition, the seroprevalence was assessed through December 9, 2021, so the results certainly reflect an underestimation of the population immunity now, after the fourth wave. The omicron variant has been associated with high transmissibility, which in combination with neutralization resistance has translated into high rates of reinfection.

The fact that many infections with the omicron variant probably occurred in persons who had been previously vaccinated or previously infected with other variants has substantial immunologic consequences. In persons who have a breakthrough infection (after vaccination), the multiple exposures to spike antigen result in high titers of antibodies.[8,9] A similar response occurs in those who are reinfected. In addition, Covid-19 vaccines continue to be deployed at increasing levels in countries with a high seroprevalence, such as South Africa. Both B-cell and T-cell responses to vaccines, even single vaccine doses, are magnified in persons who have been previously infected with SARS-CoV-2, as compared with the responses in persons who have not been previously infected.[10] This finding may have important implications for severe disease in undervaccinated regions of the world, where deployment of even single Covid-19 vaccine doses may benefit public health.

In undervaccinated regions, the long-term sequelae of widespread SARS-CoV-2 infection, including asymptomatic infection, may turn out to be substantial. Also, we know so little about prolonged illness ("long Covid"), and deciphering the consequences will be challenging when entire countries may be at risk for long-term effects of Covid-19. As we move forward, understanding Covid-19 immunity and its effects on subsequent acute severe illness and on prolonged illness may be complicated, given that large swaths of populations will have had Covid-19 (perhaps more than once) or will have been vaccinated against Covid-19 or both. At this time, undervaccination largely overlaps with countries that are already burdened by constrained health care services. If longer-term effects result from our failure to expeditiously vaccinate the populations of these countries and to prevent Covid-19 and its complications, then shame on us all.

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