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Omicron severity: milder but not mild

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In *The Lancet*, Nicole Wolter and colleagues[1] report data from more than 11 000 individuals (>80·0% aged 19–59 years; 55·9% women) with COVID-19 in South Africa indicative of significantly reduced odds of hospital admission for patients infected with the omicron SARS-CoV-2 variant of concern (B.1.1.529) versus other SARS-CoV-2 variants during the same period (Oct 1–Nov 30, 2021; adjusted odds ratio [aOR] 0·2, 95% CI 0·1–0·3) and significantly reduced odds of severe disease among patients infected by the omicron variant than among patients infected with the delta variant (B.1.617.2) in earlier epidemic waves (aOR 0·3, 0·2–0·5). These useful findings—derived from national-level COVID-19 hospital surveillance data linked with case, laboratory, and genomic data—represent a reassuring confirmation of early indicators that the omicron variant might lead to less severe disease and societal disruption, and have a reduced effect on hospital resources, than variants that dominated earlier pandemic waves. In the absence of widespread genotyping of confirmed SARS-CoV-2 infections, Wolter and colleagues[1] used amplification failure of the spike gene (S gene target failure [SGTF]) on the TaqPath PCR assay as a proxy for the omicron variant. SGTF is a reasonable marker for the omicron variant given that other circulating variants did not have this characteristic during the period of study.[1] In the context of expanding omicron variant epidemics, the level of generalisability of these South African data to other jurisdictions and timepoints is of paramount global importance.

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If this reduction in the risk of severe disease with the omicron variant, similar to that observed in England,[2] could be attributed to lower intrinsic virulence, it would provide reassurance to the public and health authorities that the recent alarming spike in COVID-19 case numbers observed globally would not translate to unmanageable increases in hospitalisations, with implications for the tightening or relaxation of disease control policies. However, South Africa has had repeated waves of infection and the extent to which this factor could explain the reduced effect of SGTF infections in late 2021 is unclear. SARS-CoV-2 reinfections are milder on average than primary infections,[3] and, by December, 2021, more than 70% of South Africans had existing anti-SARS-CoV-2 antibodies as a consequence of either natural infection or vaccination.[4] In the study by Wolter and colleagues,[1] the odds of previous infection were around 23-times higher in SGTF-infected versus delta variant-infected patients, which could be due to the omicron variant's capacity for immune escape that could increase the proportion of milder reinfections.[5] The possibility of some patients being hospitalised with, rather than for, SARS-CoV-2 infection could also affect severity analyses given near universal, pre-hospitalisation COVID-19 testing and the increasing population prevalence of infection.[6]

In an attempt to disentangle intrinsic severity from population immunity, Wolter and colleagues[1] analysed disease severity by comparing contemporaneous, hospitalised individuals with the omicron (SGTF) versus other variants (non-SGTF) using a composite measure of severity, which included admission to an intensive care unit, acute respiratory distress, oxygen treatment, and death.[1] This analysis was inconclusive, possibly due to the small number of severe outcomes; however, there is biological plausibility for some reduction in the intrinsic severity of omicron infections, as indicated by laboratory studies that report reduced pathogenesis in an animal model[7] and lower replication competence in human lung cells for omicron versus other variants.[8]

Knowing how frequently omicron causes severe disease is important. But even a milder average clinical

presentation could be offset by an increased incidence of infection with the omicron variant, with the potential for considerable societal disruption through sickness, lost productivity, and distress, and the exertion of additional pressure on health-care systems due to staff absences. For example, on Jan 6, 2022, it was estimated that one in 25 individuals in the UK had symptomatic COVID-19.[9] Self-isolation of cases, and either voluntary or mandatory quarantine of their contacts, can consequently impact large numbers of individuals.

Community epidemics of the omicron variant will probably have less of an impact on health compared with previous COVID-19 waves in most locations because of increased levels of population immunity and the possible reduced intrinsic severity of omicron infections. Nonetheless, in this generally young South African population, 21% of hospitalised patients infected with the SARS-CoV-2 omicron variant had a severe clinical outcome,[1] a proportion that might increase and cause substantial impact during outbreaks in populations with different demographics and lower levels of infection-derived or vaccine-derived immunity. This report of typically milder disease following infection with the omicron versus delta variant in South Africa is encouraging, but we should not assume that omicron variant epidemics will have such a low health effect elsewhere.

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Improving outcomes of men with incurable prostate cancer

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Androgen deprivation therapy (ADT) has been the standard of care for treating metastatic prostate cancer ever since the discovery that prostate cancer was an androgen-dependent disease in the 1940s. Since then, several therapeutic strategies have built on this basic principle to further improve survival, both through the use of additional systemic therapy in patients with metastatic hormone-sensitive prostate cancer (mHSPC) and with the addition of radiotherapy to the prostate in patients with low-volume mHSPC.[1] Patients with high-volume mHSPC are those with four or more bone metastases (of which at least one is beyond the axial skeleton), presence of visceral metastases, or both. Patients with low-volume mHSPC are patients without these high-risk features. Combining systemic therapies, such as docetaxel, abiraterone, enzalutamide, or apalutamide, with ADT have shown clear benefit over ADT alone, forming the basis for current management.[2–6] The demonstration of treatment intensification benefit in high-volume or high-risk disease was of little surprise given the poor prognosis and rapid progression to castration