

CORRESPONDENCE

Intrinsic Severity of the SARS-CoV-2 Omicron Variant

TO THE EDITOR: In their Perspective article, Bhattacharyya and Hanage (Feb. 17 issue)¹ observe that “viruses don’t inevitably evolve toward being less virulent; evolution simply selects those that excel at multiplying.” This statement assumes that the B.1.1.529 (omicron) variant evolved through natural selection as the virus passed from host to host.

One explanation for the sudden appearance of a substantial number of mutations in a single variant is that omicron evolved in a single immunocompromised host.^{2,3} Extensive SARS-CoV-2 evolution in immunocompromised hosts is well described.^{4,5} For the host to survive, the virus must establish détente between lethality and the host’s immune response. Reduced virulence may be a prerequisite for the host to survive long enough for the emergence of highly mutated strains with substantial immune escape. Thus, if omicron arose within a single immunocompromised host, then reduced virulence may be strongly favored by natural selection.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Although variants of concern including omicron may have emerged from

long-term infections in immunocompromised persons, selection during such within-host evolution may not necessarily produce a less virulent virus. Empirically, the B.1.1.7 (alpha) and B.1.617.2 (delta) variants, which were thought to have emerged in a similar manner, are both more virulent than their ancestors.^{1,2} And although omicron is less virulent than delta,³ its immediate ancestor is not delta but a virus from earlier in the pandemic. Also, omicron remains formidable in the absence of immunity,⁴ as has been seen in Hong Kong, where low rates of previous infection — and of vaccination among the elderly — have led to a staggering case fatality ratio during the unfolding omicron surge.

Given the substantial immunopathology seen in severe Covid-19,⁵ viral determinants of severity may differ considerably in immunocompromised hosts from whom variants may emerge, as compared with a largely immunocompetent population with accumulating immunity. Furthermore, the proximal source of a variant does not determine its subsequent success, since it must compete with existing variants for transmission between individuals in a population. Since severe Covid-19 occurs in a minority of cases and late in illness after most transmission has occurred, severity probably minimally affects population-level spread.

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Since publication of their article, the authors report no further potential conflict of interest.

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