

is reinforced by the predominance of viral infections in the study by Tsalik and colleagues.<sup>1</sup> The key point is to distinguish between viral and bacterial infections.

Interestingly, we also observed a clear peak in prescription of azithromycin during the first wave of the COVID-19 pandemic in 2020 in the Alsace region (appendix), which was severely affected by high rates of SARS-CoV-2 infection. This increase in prescription of azithromycin was also due to the fact that azithromycin in combination with hydroxychloroquine was thought to have antiviral or anti-inflammatory effects at the beginning of the COVID-19 pandemic, but this was later refuted.<sup>4</sup>

The inappropriate prescription of antibiotics, including azithromycin, has important consequences. First, the use of azithromycin has been associated with selection of both macrolide and non-macrolide resistance.<sup>5</sup> Second, an increase in antibiotic resistance during the winter months due to increased prescriptions has been shown.<sup>3</sup> Finally, azithromycin can contribute to the development of *Clostridioides difficile* infection.

Even if the anti-inflammatory function of azithromycin could have a positive effect to alleviate or shorten the duration of clinical symptoms, azithromycin should not be used to treat viral infections. More tools are needed to distinguish between viral and bacterial respiratory tract infections and potentially identify other anti-inflammatory options with similar effects to azithromycin but without the associated negative consequences.

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## ACE2 binding and antibody evasion in enhanced transmissibility of XBB.1.5

SARS-CoV-2 subvariants BQ.1.1 and XBB.1 have been circulating globally with superior growth advantages over most omicron mutants (appendix p 5). However, XBB.1.5, a subvariant of the recombinant mutant XBB, has shown a substantial growth advantage compared with BQ.1.1 and XBB.1. Because of its enhanced transmissibility, XBB.1.5 has rapidly become the dominant SARS-CoV-2 strain in the USA and is highly likely to cause the next global wave of COVID-19 (appendix p 5).<sup>1</sup> XBB and XBB.1 has already been shown to be extremely evasive against the neutralisation of plasma and serum from vaccinated or convalescent individuals and monoclonal antibodies (mAbs), with a greater evasive ability than the BQ.1.1 variant.<sup>2–5</sup> Compared with XBB.1, XBB.1.5

carries a Ser486Pro mutation on the spike protein, a rare two nucleotide substitution compared with the ancestral strain (appendix p 5). The mechanism behind the rapid transmission of XBB.1.5, especially the effect of Ser486Pro, requires immediate investigation.

We used vesicular stomatitis virus-based pseudovirus neutralisation assays to evaluate the neutralisation titres against XBB.1.5 of convalescent plasma from individuals who had received three doses of CoronaVac (Sinovac) before BA.1 (n=50), BA.5 (n=36), or BF.7 (n=30) breakthrough infection. A cohort of patients with convalescence from BA.5 breakthrough infection who had received at least two doses of BNT162b2 (Pfizer-BioNtech) or mRNA-1273 (Moderna) is also included in the analysis (n=10). Human ACE2 (hACE2)-binding affinity of XBB.1.5 receptor-binding domain was compared with that of XBB.1, BQ.1.1, and BA.2.75 using surface plasmon resonance. Plasma samples associated with CoronaVac were collected on average 27 days (SD 8) after hospital discharge (appendix pp 7–8). Plasma samples associated with the mRNA vaccine were collected within 2–3 weeks after hospital admission (appendix pp 7–8). The absence of BQ.1.1 breakthrough infection in individuals who were convalescent is a limitation of the ability of this study to estimate the scale of immune evasion of XBB.1.5 for this group.

Plasma samples from individuals who had received three doses of CoronaVac and had a BA.1, BA.5, or BF.7 breakthrough infection showed a substantial decrease in plasma 50% neutralisation titre (NT<sub>50</sub>) against XBB.1 and XBB.1.5 compared with that against B.1 (ASP614Gly) variant (figure A). Plasma from patients who received CoronaVac and had a BA.5 breakthrough infection showed a 44-times lower NT<sub>50</sub> against XBB.1 compared with the NT<sub>50</sub> after B.1. The decrease was 40-times lower for XBB.1.5. For patients who



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## Enhanced transmissibility, infectivity, and immune resistance of the SARS-CoV-2 omicron XBB.1.5 variant

In late 2022, the SARS-CoV-2 omicron BQ.1 and XBB lineages, characterised

by amino acid substitutions in the spike (S) protein that increase viral fitness, had become predominant in the western (BQ.1) and eastern (XBB) hemispheres.<sup>1,2</sup> The BQ.1 lineages are descendants of BA.5, whereas the XBB lineage is the recombinant of two highly diversified BA.2 lineages.<sup>2</sup>

In 2022, we elucidated the characteristics of a variety of newly emerging SARS-CoV-2 omicron subvariants.<sup>1–6</sup> At the end of 2022, the XBB.1.5 variant, a descendant of XBB.1 that acquired the S:5486P substitution, emerged and is rapidly spreading in the USA (appendix pp 6–7), and is the latest variant of concern.<sup>7</sup> Although the features of XBB.1.5 were reported by Yue and colleagues,<sup>8</sup> a comprehensive understanding of the virological characteristics of newly emerging variants is needed for sustained global health. Our epidemic dynamics analysis (appendix pp 6–7) revealed that the relative effective reproduction number ( $R_e$ ) of XBB.1.5 is 1.2 times greater than that of the parental XBB.1, and XBB.1.5 is outcompeting BQ.1.1, the predominant lineage in the USA as of December, 2022 (appendix pp 6–7). Our data suggest that XBB.1.5 will rapidly spread worldwide in the near future (appendix pp 6–7).

We next investigated the virological features of XBB.1.5. Yeast surface display assay showed that the dissociation constant value of XBB.1.5 S receptor-binding domain from the human ACE2 receptor is significantly (4.3 times) lower than that of XBB.1 S receptor-binding domain (appendix pp 6–7). Experiments using lentivirus-based pseudoviruses also showed approximately 3-fold increased infectivity of XBB.1.5 compared with XBB.1 (appendix pp 6–7). These results suggest that XBB.1.5 exhibits a remarkably strong affinity to the human ACE2 receptor, which is attributed to the S486P substitution. Moreover, neutralisation assay revealed that XBB.1.5 was robustly

resistant to BA.2 breakthrough infection sera (41-fold versus B.1.1, 20-fold versus BA.2) and BA.5 breakthrough infection sera (32-fold versus B.1.1, 9.5-fold versus BA.5; appendix pp 6–7).

During investigations, we observed that a subset of the XBB.1.5 variant reverted the deletion of 144Y in S (S:Y144del; appendix pp 6–7). As we previously showed that the S:Y144del mutation confers an increased immune escape capability,<sup>2</sup> we hypothesised that the reversion of S:Y144del (ins144Y) affects the virological features of XBB.1.5. However, XBB.1.5 without S:Y144del (XBB.1.5 + ins144Y) exhibited a lower  $R_e$  compared with the original XBB.1.5 (appendix pp 6–7). Lentivirus-based pseudovirus assays showed that the 144Y insertion increased the infectivity of XBB.1 but did not affect the infectivity of XBB.1.5 (appendix pp 6–7). Additionally, neutralisation assays showed that the 144Y insertion significantly increased the sensitivity to BA.2 and BA.5 breakthrough infection sera (appendix pp 6–7). Altogether, our data suggest that the reversion of S:Y144del does not improve the viral properties of XBB.1.5, including fitness.

In summary, our results suggest that XBB.1.5 is the most successful XBB lineage as of January, 2023, as it has acquired the S:5486P substitution, which enhances its binding affinity to the ACE2 receptor without compromising its remarkable immune resistance. Our data suggest that these virological features result in greater transmissibility.

We declare no competing interests. KU and JI contributed equally.

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