Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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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.[1,2] The BQ.1 lineages are descendants of BA.5, whereas the XBB lineage is the recombinant of two highly diversified BA.2 lineages.[2]

In 2022, we elucidated the characteristics of a variety of newly emerging SARS-CoV-2 omicron subvariants.[1–6] At the end of 2022, the XBB.1.5 variant, a descendant of XBB.1 that acquired the S:S486P substitution, emerged and is rapidly spreading in the USA (appendix pp 6–7), and is the latest variant of concern.[7] Although the features of XBB.1.5 were reported by Yue and colleagues,[8] 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,[2] 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:S486P 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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Randomised controlled trials for mpox in endemic countries

We agree with the recent Personal View from David A Lindholm and Andre C Kalil[1] that high-quality clinical trials are crucial to guide clinical decision making and to inform public health responses during emerging infectious disease outbreaks. We would like to make some additional observations regarding the clinical trial landscape for mpox (formerly known as monkeypox).

The urgent need for high-quality evidence of treatment had preceded the emergence of mpox in high-income countries. It is saddening that mpox had only become a topic of interest once transmitted outside of Africa.[2] In addition to the North American trials described by Lindholm and Kalil,[1] the first treatment trial for mpox was the PLATINUM trial in the UK (ISRCTN17461766) and plans for other European trials are in progress. Importantly, the design of these randomised controlled trials has benefited significantly from research in endemic settings, including preparatory research for the PALM007 trial (NCT05559099) and from an expanded access programme in Central African Republic.[3]

Although the authors were right that evidence from randomised controlled trials in high-income settings might help in advocating for access to drugs in low-income and middle-income countries, it might be inaccurate to extrapolate trial outcomes from high-income countries that are affected by clade IIb to other areas where the clade, route of transmission, patient population, and clinical picture are different.[4] It is therefore imperative that clinical trials are also led by and conducted in these regions and that drug pricing and availability (which are currently glossed over) are addressed. In the context of a declining incidence of clade IIb monkeypox virus, work led by endemic countries might have the best possibility of advancing the evidence base for mpox treatment.

Several countries have planned or commenced randomised controlled trials of tecovirimat, which is a promising commitment to science during outbreaks. However, as the authors suggest, work is needed to improve the speed at which trials can be started. In addition to the suggestions made for improving trial networks and infrastructure, streamlining and simplifying regulatory requirements[5] so that they are fit for purpose is likely to have a substantial influence on the ability of trials to recruit meaningful numbers of participants given the specific challenges that outbreaks present—ie, short timeframes and an unpredictable geographical dispersion of cases.

AR, JD, RH, PH, and LP are investigators on the PLATINUM trial; AR and JD are investigators on an expanded access protocol for tecovirimat in Central African Republic; and JD is an investigator on the PALM007 trial.

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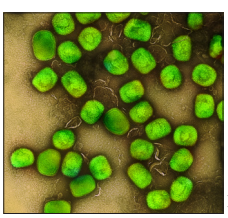
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