Replicative capacity of SARS-CoV-2 omicron variants BA.5 and BQ.1.1 at elevated temperatures

After the SARS-CoV-2 omicron variants replaced the delta variant (B.1.617.2), omicron subvariants, including BQ.1.1 and XBB, emerged and became the dominant strain worldwide. Although the omicron subvariants are more immunoevasive than earlier variants,[1,2] their virological characteristics, such as replicative capacity in respiratory organs during pyrexia,[3] are not fully understood.

We compared the replicative capacity of B.1.617.2, BA.5, and BQ.1.1 during pyrexia by using human alveolar epithelial cells (AECs) in an air–liquid interface culture, which were generated from induced pluripotent stem cells. Human AECs were infected with 1×10^4 50% tissue culture infectious dose ($TCID_{50}$) of B.1.617.2, BA.5, and BQ.1.1, and incubated at two different temperatures, 37°C (normal human body temperature) and 40°C (elevated human body temperature during illness). Samples were collected daily from the apical surface of the AECs up to 4 days post infection (dpi) for viral titration. All three variants had similar growth kinetics on human AECs at 37°C, reaching peak titres of $10^{7.5}$–$10^{8.5}$ $TCID_{50}$/mL at 2 dpi (appendix p 2). Notably, although the viral titres of B.1.617.2 at 2 dpi were 10 times lower at 40°C ($10^{6.5}$ $TCID_{50}$/mL) than at 37°C ($10^{8.2}$ $TCID_{50}$/mL), viral titres of BA.5 were 1000 times lower at 40°C ($10^{4.6}$ $TCID_{50}$/mL) than at 37°C ($10^{7.5}$ $TCID_{50}$/mL), and BQ.1.1 was unable to replicate at the higher temperature in human AECs (appendix p 2).

In Vero E6 cells expressing *TMPRSS2* (VeroE6/*TMPRSS2*), the three SARS-CoV-2 variants had similar replication kinetics at 37°C to those in human AECs at the same temperature, with peak titres at 2 dpi (appendix p 1). Virus-infected VeroE6/*TMPRSS2* cells grown at 37°C were dead by 3 dpi due to virus growth. At 40°C in VeroE6/*TMPRSS2* cells, the titre of B.1.617.2 was again 10 times lower than that at 37°C (appendix p 1). The virus titres for BA.5 and BQ.1.1 were also substantially reduced at 40°C compared with titres at 37°C, showing that the replicative capacities of BA.5 and BQ.1.1 were restricted at the higher temperature.

Our data show that omicron variants—especially BQ.1.1—cannot replicate efficiently at high temperatures, unlike B.1.617.2. Because pyrexia is one of the most common symptoms in patients with SARS-CoV-2 infection (including the omicron variant), elevated body temperature during the illness might substantially restrict BA.5 and BQ.1.1 replication in the lungs and could have an important role in limiting disease severity caused by the omicron variants. Thus, BA.5 and BQ.1.1 show lower pathogenicity than B.1.617.2. Further study is needed to reveal the determinants responsible for the temperature sensitivity of SARS-CoV-2 variants, which could lead to a better understanding of viral pathogenesis.

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See **Online** for appendix