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Study suggests omicron subvariant causes enhanced fusion with human lung cells

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New research shows that the recently-emerged BA.2.86 omicron subvariant of the virus that causes COVID-19 can be neutralized by bivalent mRNA vaccine-induced antibodies in the blood, which explains why this variant did not cause a widespread surge as previously feared.

However, the study in cell cultures showed this SARS-CoV-2 variant can

infect human cells that line the lower lung and engage in virus-host cell membrane fusion more efficiently, two features linked to severe disease symptoms. The study is published in the journal *Cell*.

The BA.2.86 variant of omicron is the ancestor of the currently dominating JN.1 and has about 60 more spike protein mutations than the original, or parent, coronavirus, including over 30 more than its close omicron relatives—the early BA.2 variant and the recently dominant XBB.1.5 variant among them.

These mutations led scientists to worry that so many changes would make the variant as tough to contain as the initial omicron outbreak in 2021–22.

"We found that, surprisingly, despite all those 60 mutations combined together, BA.2.86 is not as immune-evasive as the XBB.1.5 variant, which until recently had been dominating the pandemic for months. That's good news," said Shan-Lu Liu, senior author the study and a virology professor in the Department of Veterinary Biosciences at The Ohio State University.

"But BA.2.86 appears to have increased infectivity of human lung epithelial cells compared to all omicron variants, so that's a little worrisome. And, consistent with infectivity, it also has increased fusion activity with human lung epithelial cells," said Liu, also a professor in the Department of Microbial Infection and Immunity. "That raises a potential concern about whether or not this virus is more pathogenic compared to recent omicron variants."

The published findings coincide with reports from the Centers for Disease Control and Prevention that after a brief increase in BA.2.86 infections, its derived sublineage JN.1 rapidly gained ground in the United States, responsible for an estimated 44% of COVID-19 cases as

of Dec. 23, 2023.

First detected in July in Europe and the Middle East, BA.2.86 and its sublineages have since been spreading with increasing frequency in different parts of the world. On Nov. 22, the World Health Organization classified BA.2.86 and sublineages as "variants of interest."

The Ohio State researchers analyzed neutralizing antibodies in blood serum samples from health care professionals who had received three monovalent vaccine doses or two monovalent vaccines followed by one bivalent vaccine booster, and from first responders who had COVID-19 infections during the wave dominated by the XBB.1.5 variant.

They compared the ability of neutralizing antibodies to block infection by BA.2.86, an XBB-derived variant known as FLip, the parent virus and several omicron variants.

Overall, antibodies produced by serum from the bivalent vaccine-dosed health care professionals were more efficient at neutralizing BA.2.86 than they were at neutralizing other omicron variants, including XBB.1.5. In contrast, the three monovalent vaccines and previous XBB.1.5 infection were barely effective in blocking infection by BA.2.86.

"People who have had a COVID-19 infection should remember that omicron variants are less virulent compared to prior variants such as delta, meaning they don't make most people very sick," Liu said. "If you have less severe disease, the antibodies generated by infection are low—almost 10-fold lower than vaccine-induced antibodies. That is why you cannot rely on natural infection alone for immunity.

"While bivalent vaccine can still neutralize BA.2.86, the efficiency is clearly reduced. Therefore, it is important to get the newest booster

vaccine, which is formulated with only XBB.1.5 and has been shown to be effective against BA.2.86," Liu added.

However, the researchers were surprised to find that a monoclonal antibody known as S309, which has been shown to inhibit almost all other major omicron variants, does not neutralize BA.2.86. Molecular modeling revealed that some of the BA.2.86 mutations in the spike protein might have changed the conformation and rendered S309 unable to neutralize the new variant, Liu said.

Additional experiments pointed to the potential for BA.2.86 to be more likely to cause severe disease than its omicron relatives. Researchers found BA.2.86 was more efficient at infecting a cell line derived from the human lower airway epithelium in the lung.

Infection of these cells is greatly facilitated through a cell surface protein, known as TMPRSS2, to promote membrane fusion, and this protein is a known contributor to SARS-CoV-2 infection and disease symptoms in the respiratory tract.

First author Panke Qu, a graduate student in Liu's lab, conducted the cell-culture studies using pseudoviruses—a non-infectious viral core surrounded by different SARS-CoV-2 spike proteins on the surface structured to match known variants.

"Because we used a pseudovirus, we need to confirm these findings using the real virus," said Liu, also associate director of Ohio State's Center for Retrovirus Research and a program co-director of the Viruses and Emerging Pathogens Program in Ohio State's Infectious Diseases Institute.

"But from our past experience, we know that the infectivity in human epithelial cell lines provides very important information. The concern is

whether or not this variant, as well as its descendants including JN.1, will have an increased tendency to infect human lung epithelial cells similar to the parental virus that launched the pandemic in 2020."

Liu noted that other labs have recently suggested that JN.1, one of the fastest-growing descendants of BA.2.86, is much more resistant to neutralizing antibodies that are effective against BA.2.86.

"We know that coronaviruses are prone to viral recombination, which can lead to new variants with huge numbers of mutations that could have increased immune evasion but also disease severity," he said. "That's why surveillance of the variants is still very important, even though we are in the end of year four of the pandemic."

Additional co-authors, all from Ohio State, are Kai Xu, Julia Faraone, Negin Goodarzi, Yi-Min Zheng, Claire Carlin, Joseph Bednash, Jeffrey Horowitz, Rama Mallampalli, Linda Saif, Eugene Oltz, Daniel Jones and Richard Gumina.

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