Influenza viruses can use a second entry pathway to infect cells, study shows

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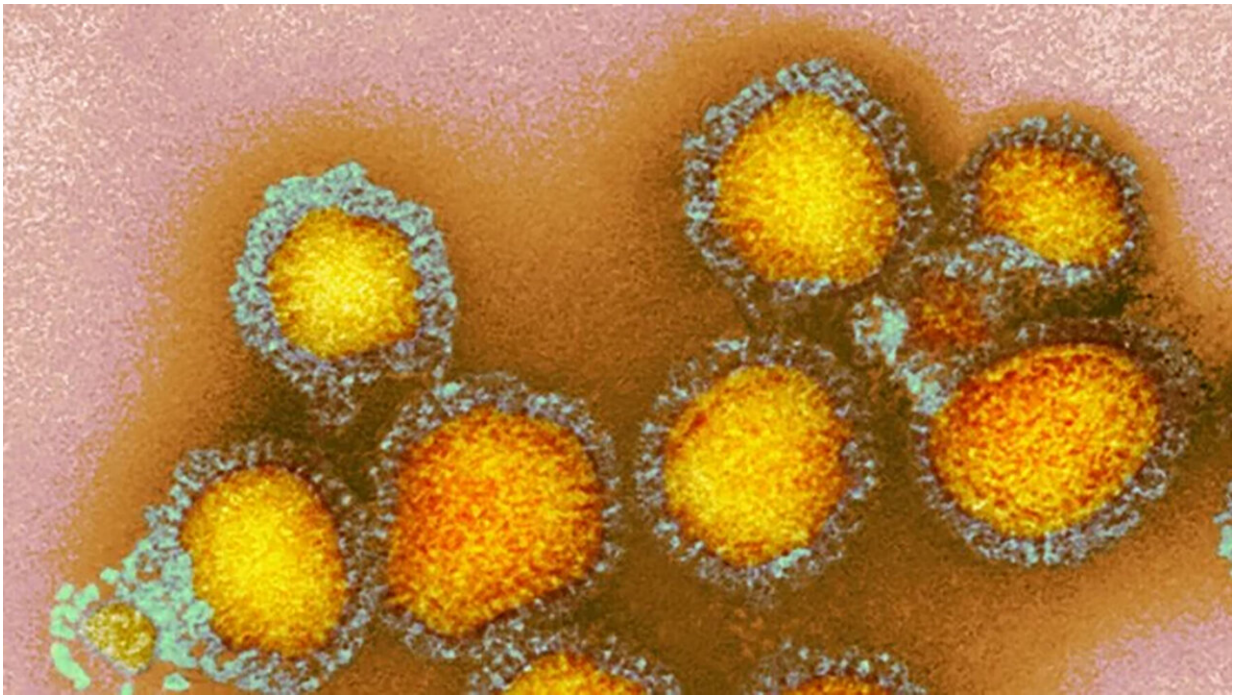

Electron microscopy image of influenza viruses. Credit: CDC/Science Photo Library

Most influenza viruses enter human or animal cells through specific pathways on the cells' surface. Researchers at the University of Zurich have now discovered that certain human flu viruses and avian flu viruses can also use a second entry pathway, a protein complex of the immune system, to infect cells. This ability helps the viruses infect different

species—and potentially jump between animals and humans.

The majority of type A influenza viruses circulating in birds and pigs aren't normally a health risk for humans. However, the viruses may pose a threat if there is an outbreak like the one currently in dairy cattle in the US or during seasonal epidemics. In rare cases, a virus can jump from animals to humans—with potentially devastating consequences such as a global pandemic.

The paper is published in the journal *Nature Microbiology*.

Additional receptor offers alternative entry pathway

Most influenza viruses enter host cells by using their envelope proteins, which stand up from the surface like spikes. The so-called hemagglutinin binds to sialic acid, a chemical group on the surface of human cells and the cells of various animal species. An international research team led by Professor Silke Stertz from the Institute of Medical Virology at the University of Zurich (UZH) has now shown that flu viruses also have a second method to infect host cells.

"Human influenza A viruses of subtype H2N2 and related H2N2 avian influenza viruses can enter cells through a second receptor. They use an alternative entry pathway," says Stertz.

The researchers found that hemagglutinin also binds to MHC class II protein complexes. These complexes on the surface of certain immune and respiratory cells are responsible for differentiating between the body's own cells and foreign cells.

"We found that MHC class II complexes in humans, pigs, ducks, swans and chickens allow viruses to enter cells, but not those in bats," says Stertz.

Transmission from animals to humans likely

This dual ability to infect cells was observed in lab-grown cell lines and human airway cultures. How well the viral receptor fits onto the cell surface structures plays a crucial part in determining which host species and tissues are infected and ultimately how severe the infection will be. Receptor specificity also influences whether a virus is able to infect different animal species or even humans (zoonosis).

"Our finding shows that influenza viruses can adapt to use different entry pathways. This might influence their ability to infect different species and potentially jump between animals and humans," emphasizes the UZH virologist.

The risk that avian, swine and other animal influenza viruses could trigger a flu pandemic in humans may thus be greater than previously assumed. The ability to use MHC class II proteins for cell entry could have been one of the reasons why H2N2 influenza viruses emerged as a pandemic virus in Asia back in 1957. This is another good reason to step up global influenza surveillance in both animals and humans.

More information: Umut Karakus et al, MHC class II proteins mediate sialic acid independent entry of human and avian H2N2 influenza A viruses, *Nature Microbiology* (2024). DOI: 10.1038/s41564-024-01771-1

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