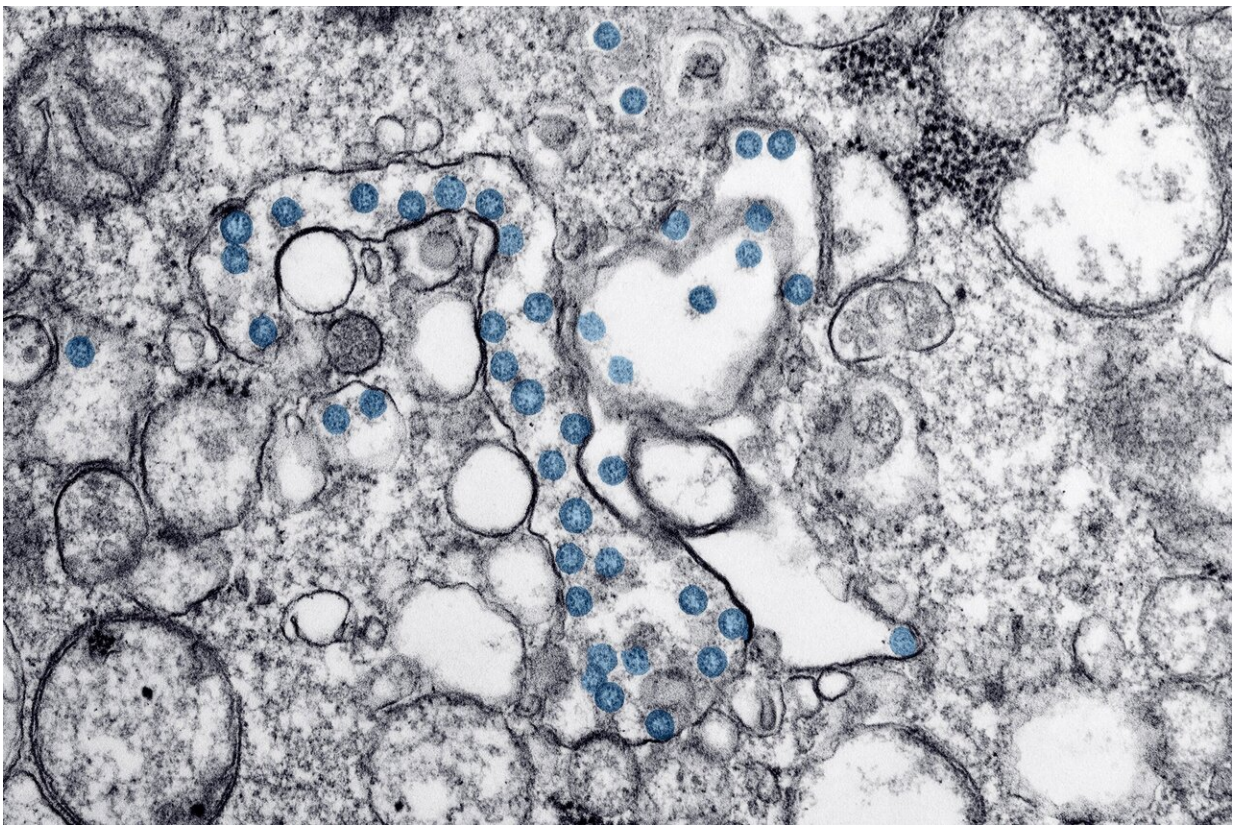
A 2014 seal flu illustrates how avian flu viruses can adapt to spread between mammals

October 7 2020



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In 2014, an avian influenza virus caused an outbreak in harbor and gray seals in northern Europe, killing over 10% of the population. In a study

appearing October 7 in the journal *Cell Host & Microbe*, researchers pinpoint the mammalian adaptation mutations that appeared during the outbreak in seals. They show that these mutations also made the virus transmissible via the air in ferrets and that similar mutations play a recurring and consistent role in making avian influenza viruses more transmissible between other mammal species.

"Usually, these occasional introductions of avian influenza viruses in seals, like in humans, are 'dead ends' because the virus is not transmissible from one individual to another," says first author Sander Herfst, an assistant professor of Molecular Virology and Virus Evolution at Erasmus MC. "However, sometimes these viruses adapt to the new host and acquire the ability to be transmitted between individuals."

The strain of avian influenza virus responsible for the outbreak, of the H10N7 subtype, first caused viral infections in harbor and gray seals along the coast of western Sweden and eastern Denmark in spring of 2014, killing more than 500 individuals. From there, it spread south toward the coasts of western Denmark and Germany, and finally the Netherlands, resulting in the death of an additional roughly 2,000 seals. Researchers believe the initial outbreak was likely caused by a seal coming into contact with birds or their droppings, but how it passed between seals is unknown.

"Transmission from seal to seal is likely to have occurred via aerosols or respiratory droplets, most probably whilst the seals are resting on land. However, direct contact transmission between seals can also not be excluded because seals are highly social and interact with each other regularly," says Herfst.

The seal outbreak therefore provided an opportunity for researchers to study how influenza A viruses, which are known for their high inter-species transmission, may jump across mammal species. Herfst and his

colleagues collected both avian and seal-adapted variants of the virus that caused the 2014 outbreak and measured their transmissibility between ferrets, which are useful model organisms for this research because viruses that are spread through the air between ferrets are likely also transmissible between humans and other mammals.

"We found that the seal-adapted virus was efficiently transmitted through the air via aerosols or droplets between ferrets, whereas the avian virus was not," Herfst says. "These findings suggest that the mutations the avian virus underwent once it took hold within the seal population have allowed it to become transmissible via the air between mammals."

In their investigations of the mutations to the seal virus and associated phenotypes that resulted in efficient transmission between ferrets, Herfst and his team found key mutations in the virus hemagglutinin—a protein on the surface of influenza viruses that plays an important role in binding to host cells. These changes, they say, affected the stability of the hemagglutinin and in addition led to the virus preferring to bind to mammal virus receptors in the respiratory tract, rather than avian. Interestingly, these hemagglutinin preference mutations occurred in viruses isolated in the late phases of the seal outbreak, suggesting that increased adaptation to a mammalian host occurred after the virus began its initial spread.

This is not the first time these kinds of mutations have been observed in influenza viruses. In fact, they have been present in prior pandemics. "The mutations that we identified are similar to the ones acquired in 1957 in the first year of the H2N2 pandemic in humans. In addition, these same mutations were required to render highly pathogenic avian influenza viruses of the H5N1 subtype transmissible via the air between ferrets—a model organism for mammal influenza research," Herfst remarks.

No cases of seal-to-human transmission have been reported, but these findings show there are consistent viral mutations that allow avian influenza to become transmissible between mammals and that seals have the potential to become a novel reservoir for avian influenza virus.

More importantly, these results reinforce the need for proactive screening to identify viral mutants that may become highly contagious and cross the species boundary.

"Previous influenza virus pandemics; the emergence of H5N1 and H7N9 influenza viruses in humans in 1997 and 2013, respectively; the current COVID pandemic; and also the H10N7 influenza virus outbreak in seals clearly demonstrate that understanding transmissibility of viruses that circulate across animal species and start to infect humans and other hosts is critical," says Herfst. "It is important to monitor and predict which of the various zoonotic viruses have the potential to emerge in humans and start outbreaks or even pandemics. Without this knowledge we can only apply a reactive rather than a pre-emptive approach to limit the impact of emerging virus infections, as is currently done for the COVID pandemic."

More information: *Cell Host & Microbe*, Sander Herfst et al.: "Hemagglutinin traits determine transmission of avian A/H10N7 influenza virus between mammals" www.cell.com/cell-host-microbe … 1931-3128(20)30466-2 , DOI: 10.1016/j.chom.2020.08.011

Provided by Cell Press