Bird flu mutation study offers vaccine clue

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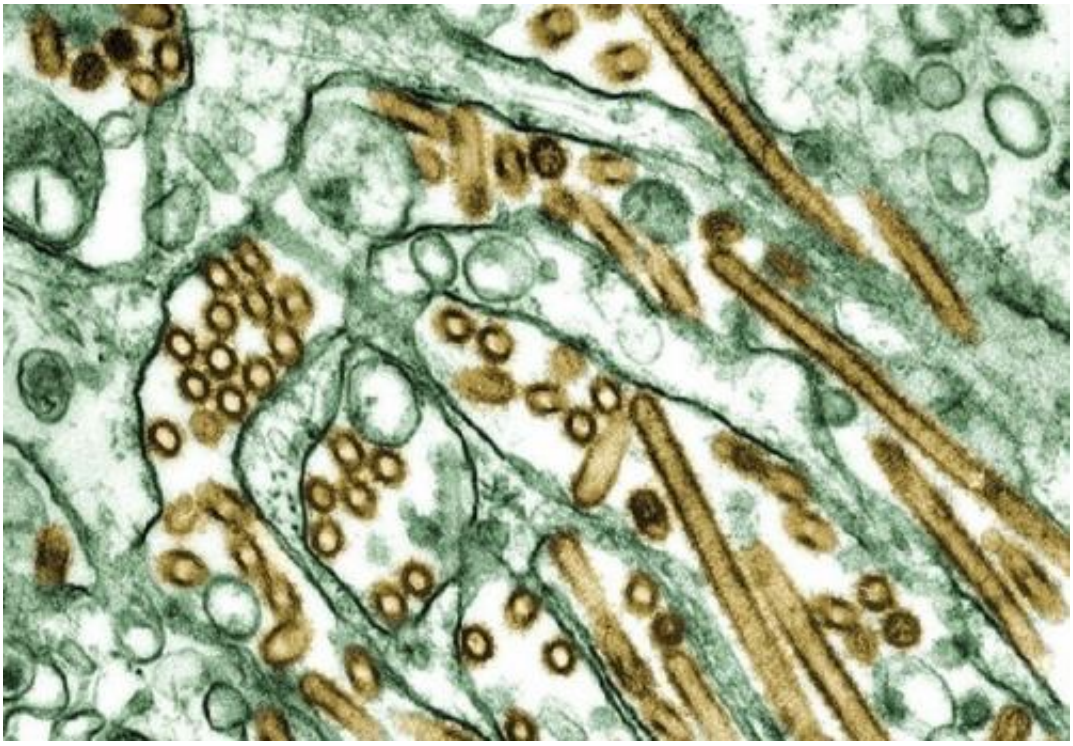

(Medical Xpress)—Scientists have described small genetic changes that enable the H5N1 bird flu virus to replicate more easily in the noses of mammals.

So far there have only been isolated cases of bird flu in humans, and no widespread transmission as the H5N1 virus can't replicate efficiently in the nose. The new study, using weakened viruses in the lab, supports the

conclusions of controversial research published in 2012 which demonstrated that just a few genetic mutations could enable bird flu to spread between ferrets, which are used to model flu infection in humans.

Researchers say the new findings could help to develop more effective vaccines against new strains of bird flu that can spread between humans.

"Knowing why bird flu struggles to replicate in the nose and understanding the genetic mutations that would enable it to happen are vital for monitoring viruses circulating in birds and preparing for an outbreak in humans," said Professor Wendy Barclay, from the Department of Medicine at Imperial College London, who led the study.

"The studies published last year pointed to a mechanism that restricts replication of H5N1 viruses in the nose. We've engineered a different mutation with the same effect into one of the virus proteins and achieved a similar outcome. This suggests that there is a common mechanism by which bird flu could evolve to spread between humans, but that a number of different specific mutations might mediate that."

Bird flu only rarely infects humans because the human nose has different receptors to those of birds and is also more acidic. The Imperial team studied mutations in the gene for haemagglutinin, a protein on the surface of the virus that enables it to get into host cells. They carried out their experiments in a laboratory strain of flu with the same proteins on its surface as bird flu, but engineered so that it cannot cause serious illness.

The research found that mutations in the H5 haemagglutinin enabled the protein to tolerate higher levels of acidity. Viruses with these mutations and others that enabled them to bind to different receptors were able to replicate more efficiently in ferrets and spread from one animal to another.

The results have important implications for designing vaccines against potential pandemic strains of bird flu. Live attenuated flu vaccines (LAIV) might be used in a pandemic situation because it is possible to manufacture many more doses of this type of vaccine than of the killed virus vaccines used to protect against seasonal flu. LAIV are based on weakened viruses that don't cause illness, but they still have to replicate in order to elicit a strong immune response. Viruses with modified haemagglutinin proteins induced strong antibody responses in ferrets in this study, suggesting that vaccines with similar modifications might prove more effective than those tested previously.

"We can't predict how bird flu viruses will evolve in the wild, but the more we understand about the kinds of mutations that will enable them to transmit between humans, the better we can prepare for a possible pandemic," said Professor Barclay.

The research was published in the *Journal of General Virology*.

More information: Shelton, H. et al. Mutations in hemagglutinin that affect receptor binding and pH stability increase replication of a PR8 influenza virus with H5 HA in the upper respiratory tract of ferrets and may contribute to transmissibility. *Journal of General Virology* (2013) doi:10.1099/vir.0.050526-0

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