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Which virus is behind the flu?

While all eyes are focused on the SARS-CoV-2 pandemic, another virus currently circulating in Europe hits the poultry industry seriously. Hundreds of thousands of birds had to be culled this winter in order to control this epizootic. The pathogen responsible for this animal disease is an influenza virus. Other influenza viruses cause disease in pigs or "flu" in humans. What is the relationship between these different influenza viruses?

Interview with Dr Gert Zimmer, a virologist at the Institute of Virology and Immunology (IVI) and the University of Bern.

What distinguishes influenza viruses?
The term "influenza virus" describes a wide range of viruses characterised by a genome with eight or seven segments of single-stranded RNA. Currently the influenza viruses are divided into four genera: influenza A, B, C and D, which together make up the "orthomyxovirus" family. Influenza A viruses represent the largest genus. These viruses circulate mainly in wild birds, but also occur in various mammals and humans. Influenza B and C viruses are almost exclusively human-pathogenic. Discovered only recently, the influenza D viruses mainly infect and replicate in cows, sheep and other large mammals.

Why are influenza viruses identified by the letters and numbers "Hx" and "Nx"?
Influenza A viruses are surrounded by a lipid envelope containing two protein antigens, hemagglutinin (HA) and neuraminidase (NA), which trigger the production of antigen-specific antibodies by the host's immune system. These antigens come in various subtypes, which differ serologically and phylogenetically. Eighteen different HA subtypes (H1 to 18) and eleven different NA subtypes (N1 to 11) are currently known.

In Switzerland, the H5N1 virus was detected in chickens in Zurich in November 2021 and in a grey heron and a pelican in the Dählhölzli Zoo in Bern in February 2022. What can you tell us about this virus?
The National Reference Laboratory for Poultry and Rabbit Diseases (NRGK) at the University of Zurich identified the causative agent as an avian influenza A virus of subtype H5N1. The IVI, the national reference centre for highly contagious animal diseases, then determined the amino acid sequence of the HA antigen and confirmed that this virus is a highly pathogenic H5N1 avian influenza virus.

What is meant by "highly pathogenic" or "low pathogenic"?
The terms "highly pathogenic" and "low pathogenic" refer to the pathogenicity of influenza A viruses in birds. The highly pathogenic avian influenza A viruses are virus mutants that replicate rapidly in many of the host's organs, which in poultry leads to a severe disease progression, usually with a fatal outcome. For reasons that remain unknown, highly pathogenic versions occur only in avian influenza A viruses of subtypes H5Nx or H7Nx.

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Why are we seeing recurring infections with avian influenza A viruses?
One reason for this is that avian influenza A viruses have their reservoir in wild birds. The genetic diversity of influenza A viruses in these hosts is enormous. HA subtypes H1 to H16 and NA subtypes N1 to N9 have been detected in wild birds in various combinations (e.g. H5N1, H5N8, H7N1, H9N2, etc.). Avian influenza A viruses may occasionally be transmitted from birds to mammals and humans. Usually mammals lack immunity to these viruses, as the influenza A viruses that circulate in mammals have different HA and NA subtypes.

Are there any influenza vaccines available for farm animals?
The general prophylactic vaccination of poultry against avian influenza A viruses of subtypes H5Nx and H7Nx is not permitted in Europe. This vaccination ban is based on the observation that vaccinated birds do not develop symptoms but can still excrete virus. The disease could therefore spread unnoticed. However, given the current crisis, there are considerations in France to resort to vaccination.

No licensed influenza virus vaccines for use in pigs are commercially available in Switzerland. Vaccination is possible in certain cases where a vaccine is imported from abroad, but this requires a special import permit from the IVI.

How high is the zoonotic potential of animal influenza viruses?
Scientific studies have shown that avian influenza A viruses do not replicate efficiently in humans and are not transmitted between humans. This does not mean that it is impossible for these viruses to become established some day in humans as a new host, but this would require many changes (mutations) in several viral genes. Despite these barriers, infections of humans with avian influenza A viruses have definitely occurred in the past, mostly after close contact with infected poultry. Between 2003 and 2021, WHO recorded 862 cases of infection with an Asian strain of H5N1, which was associated with a high mortality rate (56%). Fortunately, no human-to-human transmission of H5N1 occurred. The situation is different for porcine influenza A viruses. These viruses can adapt very easily to humans.

Why do pigs play a special role in the emergence of influenza pandemics?
Pigs are susceptible not only to porcine influenza A viruses but also to human and avian ones. If animals are simultaneously infected with two different influenza A viruses, an exchange of gene segments can occur. The resulting viruses are called “reassortants” and contain a combination of gene segments from both parent viruses. If this exchange affects the gene segments containing the genetic information for the HA and/or NA antigen, the reassortants may exhibit new antigenic properties to which the population has no immunity. There is then a risk that reassortants will trigger a pandemic. Well-known examples are the “Asian flu” in 1957, the “Hong Kong flu” in 1968 and the “swine flu” in 2009.

When humans get the “flu” in winter, which influenza virus is responsible?
In recent years, the “flu” has been caused by human influenza A viruses of the H1N1 and H3N2 subtypes and by influenza B viruses. Therefore, the flu vaccine given annually in autumn contains the antigens of all three virus types. As the HA and NA antigens of these viruses are subject to continuous mutations (“antigenic drift”), the vaccines are updated each year again.

What research is the IVI doing on influenza viruses?
Our goal is to develop new and improved vaccines to protect against influenza A viruses. Initial results have shown that modern vaccines can certainly prevent the excretion of highly pathogenic avian influenza A viruses of the H5Nx and H7Nx subtypes from immunized chickens. Such vaccines would not only protect poultry from the disease, but also reduce the risk of transmission to humans.

Since domesticated pigs are an important intermediate host in the emergence of pandemic influenza A viruses, we are also working on vaccines that can be administered nasally to induce a “mucosal” immune response in pigs, stopping the infection at the point of entry into the host. Another challenge is the pronounced variability of the viruses. We are therefore aiming to develop vaccines that can induce broad immunity against different influenza A viruses. A first achievement in the development of such vaccines was the finding that not only the highly variable HA antigen, but also the much more conserved NA antigen can induce a protective immune response.

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