

Patient information

Bird Flu

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Deceiving idyll?
Ducks entering the lake (Alexander Köster, 1864-1932, oil/canvas, detail)
Photograph: Ketterer Kunst, München

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Dear patient,

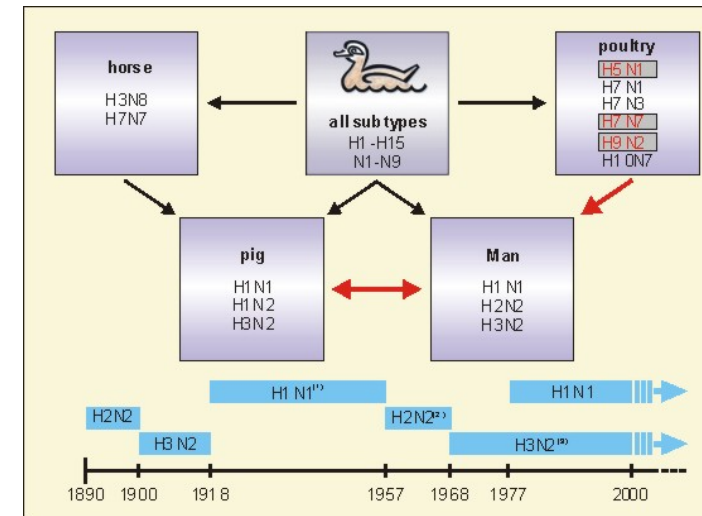
bird flu (avian influenza) is an acute and very contagious bird disease. It can take a benign course but, as avian plague, also is capable to eradicate big stocks of fowl with mortality rates of 90-100%. Bird flu/avian influenza is caused by the avian influenza virus. It was assumed that these viruses would infect birds and pigs exclusively and would not cause any harm to human beings. But in 1997 in Hongkong during a breakout of avian plague, humans also were infected with avian influenza. They developed a severe illness which proved to be fatal for one third of patients, the human bird flu (human influenza A [H5N1]). Now the threat exists that the genome of human influenza viruses, which are easily transmittable from man to man, mixes with that of the bird flu viruses which potentially lead to severe and often deadly illness. The new virus hybrid possibly would combine the features of both viruses and trigger a worldwide pandemic with several hundred millions of victims.

► What are bird flu viruses?

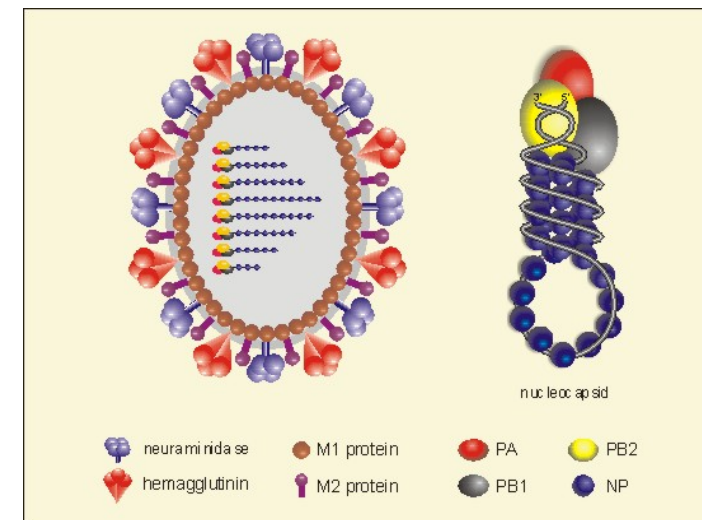
The bird flu virus belongs to the influenza type A viruses, more than one hundred mostly harmless subtypes of which predominantly occur in birds and waterfowl. The viruses probably get transmitted to domestic fowl like chicken by infected wild birds and waterfowl, particularly ducks. Some aggressive variants of these subtypes, e.g. the influenza A (H5N1) subtype detected in Hongkong in 1997, are capable to trigger avian plague in chicken and the dangerous human bird flu in human beings. Different subtypes like influenza A (H1N1) cause the classic human viral flu, others lead to respiratory tract infections in horses and pigs (picture 1). As a rule, human influenza A viruses easily transmit from man to man by airborne droplets or direct contact. They settle in the mucous membranes of mouth, nose and throat spreading from there to bronchial tubes and lungs. In birds, influenza A viruses mostly colonise lungs and intestine. Large quantities will be excreted through the cloaca and transmitted to other animals or humans by water, particulate matter, polluted equipment, bird droppings or direct contact.

► What is the difference between harmless and dangerous bird flu viruses?

Influenza A viruses consist of a **viral envelope** and the **nucleocapsid** (picture 2). Two kinds of protein molecules stick out of



Picture 1 Water fowl, particularly wild ducks are the primary reservoir for influenza A viruses being transmitted to other hosts from there. In wild ducks, the viruses proliferate in lungs and intestine and are excreted in high concentrations via the cloaca. Bird flu viruses and viruses adapted to humans may be transmitted to pigs simultaneously. Subtypes of bird flu viruses also detected in humans are marked red. The time scale indicates the subtypes of human flu. (1) Spanish flu (1918/19), (2) Asiatic flu (1957/58), (3) Hongkong flu (1968/69), (4) Russian flu (1977).



Picture 2 Schematical description of the influenza A virus and one of its eight nucleocapsid segments. The membrane proteins hemagglutinin and neuraminidase showing on the outside establish contact to the host cells. Several different proteins are surrounding the spiral RNA strand of the nucleocapsid harbouring the genetic information.

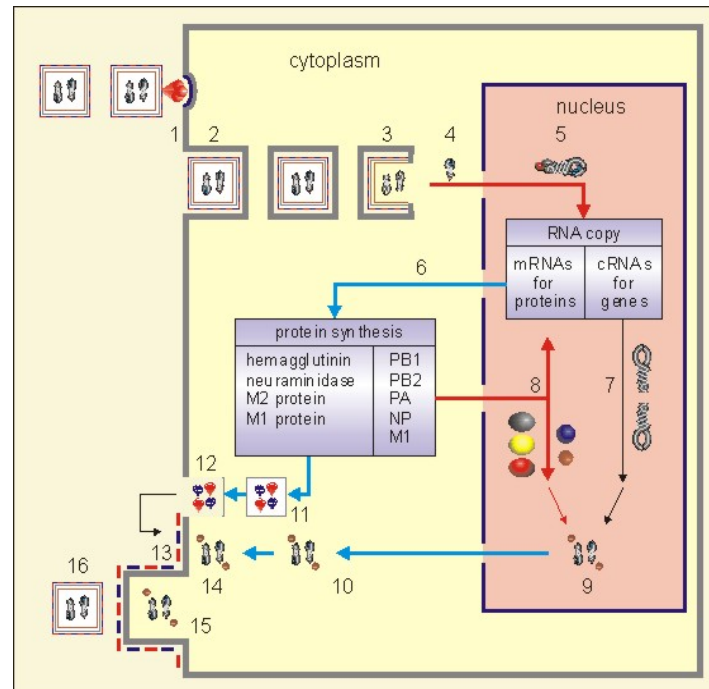
the **viral envelope** like spikes: the membrane proteins hemagglutinin and neuraminidase. There are known 15 different hemagglutinins (H1-H15) and 9 neuraminidases (N1-N9), which are used to classify the subtypes (e.g. influenza A (H1N1)). The nature of the hemagglutinin not only determines if and in which species (humans, pigs, birds) a virus is able to invade a cell, but also its pathogenicity (i.e. its ability to provoke an illness). A virus only becomes pathogenic if its hemagglutinin gets activated by proteolytic enzymes of the host cell. Therefore, the virus is able to multiply exclusively in such cells or organs which contain these special activating enzymes. The bird flu virus subtype influenza A (H5N1) exists in two variants: a harmless variant which is little pathogenic and a highly pathogenic one resulting in illness. The hemagglutinins of the latter only differ in a subtle detail leading to easier and more ubiquitous activation of the highly pathogenic variant's hemagglutinin.

After infection by the virus the cell metabolism will be triggered to exclusively produce new components for the viral offspring. As a result, the cellular protein production subsides and the cell dies (necrosis). Beforehand, the newly assembled viral offspring will be liberated. This process involves the neuraminidase membrane protein. If neuraminidase is inhibited by drugs (so called neuraminidase inhibitors like Tamiflu®), it is no longer possible for the viral offspring to detach from the cell and further dissemination in the organism will be prevented.

The **nucleocapsid** located in the interior of the virus contains the viral genome consisting of 8 ribonucleic acid (RNA) segments coding for the viral proteins. Each RNA segment is surrounded by several functional proteins either transporting the RNA into the cell nucleus or copying RNA segments (RNA dependent polymerases). These copies either as messenger RNA (mRNA) serve to synthesize the viral proteins or as genomic RNA (picture 3). The copying capacity of the polymerases i.e. the number of RNA copies available for assembly of the viral offspring is higher in heavily pathogenic variants because more infectious viruses are produced.

► How do flu epidemics and pandemics emerge?

Human Influenza A viruses give rise to global waves of flu in 10-40 year's intervals (pandemics: Spanish flu, 1918/19; Asiatic flu, 1957/58; Hongkong flu, 1968/69; Russian flu, 1977), followed by local epidemics after a 1-3 year time lag. Requirements for epidemics and pandemics are (1) infectious viruses,



Picture 3 Influenza A virus reproduction cycle: (1) The hemagglutinin anchored to the viral envelope binds to the receptors of the host cell, (2) the cell membrane folding around the virus and enclosing it. (3) The virus vesicle opens in the interior of the cell (4) releasing the nucleocapsid and (5) transporting it into the cell nucleus. Here, RNA copies are produced which are used (6) as messenger RNA (mRNA) to synthesize viral proteins or (7) as genomic RNA for the genetic material of the viral offspring. (8) Part of the viral proteins produced in the cytoplasm will be transported to the cell nucleus where they get involved in copying processes or (9) combine with the genomic RNA copies to form early stages of the viral offspring. (10) The early stages are leaving the nucleus reaching the cell membrane. (11) The viral membrane proteins manufactured in the cytoplasm are sent to the cell membrane in transport vesicles and (12) fuse with the cell membrane liberating the membrane proteins to the outside. (13) The membrane proteins get fixed to the exterior of the cell membrane forming (14) an anchor point for the early stages at the opposite interior of the cell membrane (15) bulging with the nucleocapsids and then (16) budding the new virus. The lipid envelope of the virus is derived from the cell membrane of the host cell.

An infected individual will produce about one billion of viruses daily. Of this number, about 1 % (10 millions) are infectious for the same species, for an alien host (bird/humans) just about 100. The fate of the viruses in the new host depends on the ability to run through a complete replication cycle.

(H5N1) within 14 days) but by the influenza A viruses constantly changing their genome. Thus, their nucleocapsid and membrane proteins inevitably are changed as well so that the immune defence is no longer able to recognize them.

This constant metamorphosis is caused by imprecise functioning of the viral RNA copying enzymes. They build RNA copies deviating from the original in a few selected points only (point mutations). On average, in one of every ten copies a point mutation in one of the 8 RNA segments occurs, i.e. every 10th virus produced shows a small deviation from the original. Several such mutations in a row inevitably are leading to changes in the structural details of the protein, e.g. hemagglutinin, coded by the RNA segment affected (so called antigenic drift). Therefore, flu vaccines have to be adapted annually to cover the subtype variants currently circulating in the population. The devastating Spanish flu virus, responsible for the death of more than 20 million, presumably developed from a former duck virus by a continuous sequence of such point mutations. The genome of the bird flu virus influenza A (H5N1) already has changed since 1997. From the first genotype another 15 different subtypes emerged with the Z genotype dominating and circulating in South East Asia at present.

But not only slowly by point mutations but also very rapidly new viruses pathogenic for humans and with pandemic potential may come into existence. This may happen if genome segments are exchanged in between different subtypes. If a cell gets infected by two different subtypes simultaneously, one or more of their RNA segments may be interchanged and packed in the viral offspring. So called **reassortants** are created (antigenic shift). If RNA segments of an easily transmissible, humane flu virus would be embedded in a highly pathogenic bird flu virus, a bird flu virus already infectious for humans (requirement 1) could gain the feature of easy transmission (requirement 2). Requirement 3, i.e. missing immune protection against the new reassortant, also would be complied with. The subtypes responsible for the Asiatic (H2N2) and Hongkong flu (H3N2) originated in that way. In principle, reassortants can emerge in both humans and animals. Pigs owning receptors of hemagglutinins of human as well as bird flu viruses are predestined. Close contact between poultry and pigs in agricultural environments may render possible the emergence of such reassortants.

(2) easy transmission of the viruses from man to man and (3) lack of immune protection in the population. The lack of immune protection is not caused by failure to build up a long-lasting immune defence against a flu virus (humans too are able to generate antibodies against the avian influenza A virus

► How dangerous are bird flu viruses?

In Hongkong in 1997, 18 people came down with highly pathogenic influenza A (H5N1). Six of those patients died. Ever since more, often deadly infections caused by this bird flu virus have been registered in China, Vietnam, Thailand, Cambodia and Indonesia (114 infections, 58 deaths). Because the virus has become endemic in the bird population of South East Asia in the meantime, more human infections are to be expected. An avian plague epidemic in the Netherlands triggered by subtype A (H7N7) caused non-acute illness in 83 patients with one victim dying from pneumonia. Human bird flu is not transmitted by droplets like the classical human flu, but only after close contact to sick animals. Contact to infected animals (ducks) not showing symptoms, objects contaminated with bird droppings or dust may also be a possibility. The risk of a food-borne infection seems to be of minor importance.

Human to human transmission of the pathogen may be a remote possibility, but only with the precondition of very close contact of the persons affected (household [5], mother/child [1], nurse [1]). As presently known, bird flu patients do not yet seem to pose an undue threat to hospital personnel. But, regional variants better adapting to humans and becoming easier transmissible cannot be excluded with certainty.

Since 1997, the viral pathogenicity affecting mammals (laboratory mice) has increased. The virus not only spread to several South East Asian countries during recent years, but extended its host spectra to wild cats (after feeding raw meat of infected birds), cats (experimental), pigs and particularly wild birds. It is no longer possible to prevent its spread. Migratory birds presumably introduced it from China to Mongolia, Kazakhstan, Siberia, Russia, Turkey and Eastern Europe. Thus, it also may reach the middle of Europe, predominantly posing a threat to poultry stocks.

► What to do if bird flu is suspected?

In Middle Europe, human bird flu only should be suspected in the following situations: travel to countries with documented bird flu cases 7-14 days before onset of a respiratory tract infection with high temperatures and possibly watery stools and contact (within 1 meter) to living or dead domestic poultry, ducks, wild birds or patients either with confirmed influenza A (H5N1) or respiratory tract infection of unknown origin followed by pneumonia or death. The suspected diagnosis is noti-

fiable.

If strongly suspected, a **throat swab** should be tested for H5N1 and other influenza A viruses immediately. Until completion of the test, action has to be taken to **prevent the risk of transmission** to other people. Appropriate measures are meticulous and frequent hand washing, mouth mask, avoidance of facial contacts and sharing of objects. Gatherings and shared facilities are to be avoided as well.

In cases of reasonable suspicion, **neuraminidase inhibitors** (e.g. Oseltamivir, Tamiflu®) are recommended which should be administered as early as possible (24-72 hours post infection).

Travelers to the countries of risk should be immunised against flu at least two weeks before departure. This vaccination is not capable to protect against the bird flu virus but only to prevent a simultaneous infection with human influenza A viruses. Every contact with birds and other potentially infectious material (bird droppings etc.) and consumption of only shortly cooked eggs and poultry is to be avoided. Meticulous and frequent hand washing is of importance.

► Are there immunisations against bird flu?

Immunisation against influenza A (H5N1) is not yet available. Considerable efforts are invested in its development. The influenza vaccines for prevention of classic human flu are not effective against bird flu viruses. It is not possible to create in advance a vaccine against the fictitious supervirus hybrid. It would take 6 months from appearance of the virus until mass production of the vaccine. In the meantime, it would have spread over the globe.

► Are there lab tests for bird flu?

Our laboratory offers specific molecular genetic tests (PCR) for detection of influenza A (H5N1) and other influenza A virus subtypes. Most appropriate sample material is a deep throat swab. Influenza A H5N1 has also been found in the intestines, faeces, blood and CSF. Test duration is 3-4 hours. The rapid test for influenza A virus which is recommended, too, in fact is a little faster, but not as sensitive and specific. If positive, it will demand time consuming follow-up tests. Further inquiries are welcome.

Informations for travelers to the countries concerned may be found here (in German): www.auswaertiges-amt.de, www.verbraucherministerium.de, www.fli.bund.de.