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Review of latest available evidence on risks to human health through potential transmission of avian influenza (H5N1) through water and sewage

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This document is periodically revised as more information becomes available. Questions and answers are being separately developed and will also be periodically updated. To this end, we welcome comments, which can be submitted via email to WSHavianflu@who.int

The most up-to-date version of this document can be accessed at: http://www.who.int/water_sanitation_health/emerging/h5n1background.pdf.

Purpose

The purpose of this document is to summarize the latest available evidence on avian influenza-related risks to human health associated with water resources, water supplies and sanitation (management of human excreta). It is intended to serve as the scientific basis to inform a more general briefing note, including questions and answers, directed at public health authorities, those involved in the management of water resources and supplies, and the general public. Both this document and the questions and answers will be periodically updated.

Background

There are three types of influenza viruses: A, B and C. Influenza type A viruses can infect humans, birds, pigs, horses, and other animals, but wild birds are the natural hosts for these viruses. Influenza B viruses are usually found only in humans and generally are associated with less severe epidemics than influenza A viruses. Influenza type C viruses cause mild illness in humans and are not a significant concern for human health. Only influenza type A viruses can cause pandemics and will be discussed in this document.

Within influenza A viruses, there are many different subtypes, some of which have low pathogenicity and others that have high pathogenicity. Everyone is familiar with human influenza virus, the seasonal affliction that causes symptoms such as fever, cough, sore throat and headaches. Human influenza is caused by human influenza viruses that can be transmitted between humans. Three influenza A subtypes: H1N1, H1N2 and H3N2 have caused major outbreaks in humans. The H (haemagglutinin) and N (neuraminidase) refer to certain proteins on the surface of the viruses that carry the viral receptor sites. H1N1 virus, for example, has an HA 1 protein and an NA 1 protein. Human influenza virus replicates primarily in the respiratory tract of humans (*1,2*).

Avian influenza or bird flu is less well known, although it has captured media attention in recent years. Avian influenza is an infection caused by avian influenza viruses, with transmission normally occurring between birds. In contrast to human influenza, the virus replicates in the gastrointestinal tract. Less commonly, avian influenza has infected pigs, and on rare occasions, humans (*1,2*). The subtype of avian influenza A virus known as H5N1 is very contagious among birds and can cause significant mortality in some avian species. In the rare instances that the virus is transmitted from birds to humans, H5N1 can cause pneumonia, multi-organ failure and often death. As of 24 March 2006, there have been 186 cases of transmission to humans, with 105 fatalities reported to WHO (*1,2*).

The overriding concern with respect to the H5N1 virus is that it may change into a form that is highly infectious for humans and that spreads easily from person to person. This could mark the start of a global outbreak or pandemic. No one will have immunity to the virus, as no one will have been exposed to it or developed antibodies. No vaccine with guaranteed efficacy can be prepared in advance of such an outbreak, because the causative virus does not yet exist (*1,2*). However, potential vaccines are being prepared and stockpiled in advance, in the hopes that they may match a pandemic strain.

Most cases of H5N1 infection in humans to date have occurred as a result of direct contact with poultry or with surfaces and objects contaminated by their faeces. However, concern has recently been expressed about the potential for transmission of the virus to humans through water and sewage, although no definitive cases have been reported to date.

This document examines the routes of entry of the avian influenza H5N1 virus into water and sewage, the persistence of the virus in the environment, and its possible routes of transmission to humans through water and sewage. The risk associated with selected exposure scenarios is examined and preventive and control measures are suggested.

Information on avian H5N1 virus is provided where available, but data on other avian influenza viruses are used to fill in knowledge gaps. Although the "pandemic H5N1" virus does not yet exist, it may behave like avian influenza H5N1 virus in many respects.

Based on this review, water supplies receiving treatment as recommended in the WHO Guidelines for Drinking Water Quality[1] are unlikely to pose a significant risk of infection even if infected waterfowl are present in source waters.

Routes of entry into water

Wild waterfowl are considered the natural reservoir of all influenza A viruses. Most infected birds exhibit no symptoms, even when they are excreting large quantities of infectious virus. These asymptomatic birds act as "silent" reservoirs of the virus, perpetuating its transmission to other birds (*1*).

Infected waterfowl carry avian influenza viruses in their gastrointestinal tract, where the viruses replicate (*3,4*). Birds infected with avian influenza virus shed large quantities of virus in their faeces as well as in their saliva and nasal secretions (*2*). Shedding occurs in the first two weeks of infection (*5*). The period of avian influenza infectivity in faeces and secretions depends on pH and temperature conditions, but generally four weeks after infection, avian influenza virus can no longer be detected (*5*). Ducks infected with the H5N1 virus have been found to shed the virus at high titres from the trachea as well as from the cloacae, with peak levels of virus shedding after three days (*6,7)*.

It has been shown that one infected duck excretes up to 10^{10} EID_{50} (the median egg infective dose) in 24 hours (*4*). As ducks are known to excrete 7.5–10 kg of faeces per year and geese excrete 12.5–15 kg (*8*), infected waterfowl may be able to excrete up to 3×10^9 EID_{50} per gram faeces. In a study in which ducks were infected with 10^6 EID_{50} of

[1] WHO (2004) *Guidelines for Drinking Water Quality, Third Edition*. Geneva, World Health Organization. Available at http://www.who.int/water_sanitation_health/dwq/gdwq3/en/index.html

virus in 1 ml volume, high titers of H5N1 virus were isolated from duck faeces on day 3 post-infection (*9*). Virus titres were 2.25–3.75 $\log_{10}$ EID_{50} per gram fresh faeces (*9*).

It is likely that infected droppings or other secretions from both symptomatic and asymptomatic migratory waterfowl will enter water environments where the birds gather. Avian influenza virus has been isolated from unconcentrated water from six lakes in Canada where ducks gathered and deposited large amounts of faeces (*10*); from lakes in the United States (*11,12*); and from concentrated pond water from Hong Kong (*13*). There are no quantitative data available on levels of H5N1 virus in lake water where waterfowl gather, although its detection in unconcentrated water and in small sample volumes suggests that levels are relatively high.

Besides direct deposition of faeces into lake water by migratory waterfowl, it has been suggested that faecal waste from duck and chicken farms may spread to bodies of water via wind, surface runoff or possibly enter groundwater through disposal and composting of waste on poultry farms.

Routes of entry into sewage

The H5N1 virus could potentially enter into sewage in urine or faeces excreted by infected humans or in animal waste that is combined with human sewage.

Information on the excretion of H5N1 viruses in urine or faeces by mammalian species, including humans, is exceedingly limited and unlikely to be representative of a potential future human pandemic strain. The isolation of the H5N1 virus from the faeces of a child presenting with diarrhoea followed by seizures, coma and death (*14*) suggests that the virus may be excreted by infected humans and can enter sewage in this manner. No virus was detected in the urine of this patient (*14*).

Avian influenza virus may also be shed in faeces by mammals, including livestock. The site of infection and virus replication in mammals may vary and it is important to note that both viral and host factors may influence tissue tropism (*15*) (i.e., the types of cells and tissues infected by a virus define its tissue tropism).

Persistence in water

Avian influenza viruses can persist for extended periods of time in water, although quantitative information on the subtype H5N1 is lacking. Data on other avian influenza subtypes are presented to fill the knowledge gaps.

One study (*4*) showed the avian influenza subtype H3N6 resuspended in Mississippi River (USA) water was detected for up to 32 days at 4 °C and was undetectable after 4 days at 22 °C. The data showed a decrease of about 4 logarithmic units (LU) in 32 days at 4 °C (T_{90}, the time taken to eliminate 90% of the virus in the sample, was estimated to be 8 days) and of more than 8 LU at 22 °C (estimated T_{90} = 0.5 days). In a second study (*16*), which used five low-pathogenicity avian influenza viruses (H3N8, H4N6, H6N2, H12N5, and H10N7), infectivity of virus in distilled water (initial concentration 10^6 $TCID_{50}$, or median tissue culture infective dose, per ml) was retained for up to 207 days at 17 °C and 102 days at 28 °C. The T_{90} ranged between 21 and 32 days at 17 °C and between 5 and 17 days at 28 °C, depending on the strain. In a study that showed a high level of positive water samples (23%) for a strain of influenza A virus in a lake where ducks were nesting, the proportion of positive samples remained high (14%) in the autumn after the ducks had left for migration, indicating that the virus is able to persist in water (*12*).

Other studies of the persistence of avian influenza viruses in water have shown that these viruses persist for different periods of time depending on temperature, pH and salinity. For example, one study showed that viruses survived longest (T_{90} = 17 days) at 17 °C, with low levels of salinity and a pH of 8.2 (*17*). The shortest viability was observed when virus was exposed to 28 °C with 20 ppt salinity and a pH of 8.2 (T_{90} = 1.5 days) (*17*).

Persistence in sewage, excreta and animal wastes

Studies on the survival of viruses in human faecal wastes and agricultural animal wastes have indicated that persistence is dependent on several factors, including the virus type, waste type, temperature and other environmental conditions and processes (*18*). Virus concentrations are reduced at various rates and to various extents in both human and animal waste treatment processes, depending on conditions, but they are not completely eliminated. Furthermore, virus concentrations may be enriched in certain treated or separated waste fractions (such as waste solids) by sedimentation and solid–liquid separation processes (*18*).

Little information is available on factors affecting the persistence of H5N1 virus in sewage or on the effect of waste treatment processes on H5N1 concentrations. H5N1 virus was isolated from duck faeces on day 3 post-infection (ducks had been infected with 10^6 EID_{50} of virus in 1 ml volume) at 2.25–3.75 $\log_{10}$ EID_{50} per gram fresh faeces but became undetectable after the faeces were dried overnight at room temperature (20 °C). Virus titres declined in wet faeces kept at 25 °C but remained detectable for 7 days. When the wet faeces were stored at 4 °C, the virus remained viable when testing ceased at day 20. At 37 °C, the viruses remained detectable in wet faeces until day 4 (two viruses) and day 6 (two viruses) (*9*). These results suggest that freshly deposited faeces are highly infective (at any temperature), that H5N1 in faecal deposits on land may be more rapidly inactivated than H5N1 in water and that the virus's survival decreases at higher temperatures.

H5N1 typically persists in colder temperatures and produces outbreaks during the colder months of the year (*19*). However, recent studies mentioned above have shown that current H5N1 strains survive longer in faeces at warmer temperatures than previously circulating viruses (*9*), which may explain how the virus has resurfaced in summer months in Asia.

Routes of transmission

Evidence is lacking on the mechanisms by which the avian influenza H5N1 crosses the species barrier from birds to infect humans. Human-to-human transmission of human influenza virus occurs primarily by inhalation of infectious droplets or airborne droplet nuclei, personal contact and transfer to the respiratory tract via the nose, eyes or mouth. Bird-to-human transmission of avian influenza virus is likely to encompass these routes, as well as others, including possibly, ingestion of contaminated water, although there is, as yet, no evidence of this reported (*20*).

Most cases of H5N1 infection in humans are the result of direct contact with poultry or with objects or surfaces contaminated with faeces from infected poultry (with a few cases of suspected human-to-human contact). These observations suggest either a respiratory (e.g. inhalation of infectious aerosols or droplets) or faecal–oral route of transmission from birds to humans.

There is very little information on the role of water in the transmission of influenza viruses among waterfowl or to other animals, including humans. One study (*13*) has suggested that the faecal–water–oral route is probably significant in transmission of the virus between birds, in view of the greater number of virus isolations from the cloaca than from the trachea of domestic ducks. The authors suggested that a cycle of waterborne transmission and maintenance of influenza viruses exists within the duck communities of southern China and that it is conceivable that virus transmission could occur in this manner to other susceptible animals, including humans.

This conclusion was supported by another study in which influenza A virus was isolated throughout the year from faeces and/or pond water where dabbling ducks nested in Alaska, USA; recurrent faecal contamination of pond water led to transmission of the virus to uninfected ducks (*12*). In contrast, in another study (*6*), juvenile mallards were inoculated with 23 different H5N1 influenza viruses isolated in Asia between 2003 and 2004. Viruses replicated to higher levels in the trachea than in the cloaca of both inoculated and contact birds, suggesting that the digestive tract may not be the main site of H5N1 influenza virus replication in ducks and that the faecal–oral route may not be the main transmission path.

The fact that waterfowl excrete influenza viruses into water does not confirm waterborne transmission between birds; nor does it offer an indication of the extent of the risk of infection to humans exposed to the water. Some other viruses are likewise excreted into water environments without being transmitted to a meaningful extent via that route.

The clinical presentation of infection in humans by H5N1 avian influenza virus provides additional suggestive evidence concerning routes of transmission. The frequent occurrence of diarrhoea in infected humans and the detection of viral RNA in most faecal samples tested (and infectious virus in one faecal sample) suggest that H5N1 virus may replicate in the human gastrointestinal tract (*14,20,21*). This raises the question of whether human faeces could be a source of transmission. Diarrhoea in human arising from H5N1 avian influenza appears to be more common than in influenza due to human viruses and may precede respiratory manifestations by up to one week (*21*). In fact, in the case of two children who died from H5N1 infection (*14*), both presented with diarrhoea without apparent respiratory symptoms. The observation of virus in the faeces of infected humans of course does not necessarily mean that there is a faecal–oral route of infection for humans or even a faecal–respiratory route, but it may have implications for loads in sewer systems and aerosol generation. Although symptoms of avian influenza from viruses other than H5N1 in humans include eye infections (*2*), it should be noted that patients with H5N1 avian influenza have rarely had conjunctivitis (*21*).

It is entirely possible that the H5N1 avian influenza infection process in ducks and other migratory bird species is not the same as the infection process in humans. In birds, it appears to be predominantly an enteric infection, whereas in humans (and other mammals) it may be respiratory, or enteric, or both.

Environmental exposure scenarios

Given the survival of H5N1 in the environment, several modes of environmental transmission are theoretically possible (*21*). If it is assumed that humans can be infected by the virus through both the faecal–oral and respiratory routes, potential exposure scenarios can be described, including, but not limited to, the following:

- consumption of drinking-water contaminated by the virus (e.g., untreated drinking-water drawn from a contaminated water body or from a rainwater collection system on a contaminated rooftop);
- recreational use (e.g. swimming or bathing) in contaminated water;
- exposure to virus in sewage or surface waters where sewage contaminated with virus has been discharged; and
- occupational exposure to excreta and infected animals (e.g., sewage treatment, agricultural practices).

Risk assessment / risk management related to water and sewage

Aspects of some of the exposure scenarios identified above are examined in more detail below in terms of their potential risk to humans and possible prevention and control measures.

What are the risks from influenza viruses associated with wildfowl in open drinking water 'reservoirs'

Open bodies of water will attract migrating birds, particularly waterfowl; if these birds are excreting influenza viruses at the time they are in contact with the water, there is the potential for that water to become contaminated with influenza viruses. Many variables will influence the probability of virus contamination and the persistence/survival of these viruses, including whether the stored water is on a natural flyway for waterfowl, the number of birds stopping over, the availability of food for waterfowl in that water, the time of year, temperature, pH and the length of time between deposition of faecal material and the draw off of water. The probability of having detectable levels of influenza viruses in such bodies of water is likely to be higher in the seasons when migratory birds are passing through the area.

The risk to humans will depend on a variety of factors, including the use to which the water is put, the health status of the humans (e.g. immunocompromised versus healthy), and whether or not the water is treated.

There is no available epidemiological evidence associating wildfowl excreta or death in storage reservoirs of either treated or untreated drinking water with human disease through drinking-water supply. Nevertheless, it is theoretically possible that transmission of avian influenza could occur in specific local circumstances were a series of factors to coincide. These could include wildfowl and domestic poultry contamination of storages, distribution of water without treatment (including without disinfection); and household use that gave rise to an infectious exposure, possibly through the oral ingestion of contaminated water, or conjunctival inoculation through face washing with contaminated water or contaminated hands.

However, water supplies receiving treatment as recommended in the WHO Guidelines for Drinking Water Quality[2] are unlikely to pose a significant risk of infection even if infected waterfowl are present in source waters. Moreover, a quantitative risk assessment for avian influenza infection of humans through consumption of contaminated drinking water in the Netherlands, estimated a daily risk of infection to be below health-based standards (*22*).

Prevention and control measures can be suggested to minimize, if not eliminate, the risk from the consumption of contaminated water. If the water from open water reservoirs is to be used for a potable water supply, treatment as recommended by the WHO Guidelines is strongly recommended. Due to their structure, influenza viruses are relatively susceptible to disinfectants, including oxidizing agents such as chlorine as well as enzymes like proteases, peptidases, neuraminidases and haemagglutinases. They are also readily inactivated by heating, so boiling would also be effective[3].

Authorities charged with managing any potential risk may consider ensuring chlorination or alternative residual disinfectant residuals be maintained throughout distribution. For effective disinfection of adequately pre-treated water, there should be a residual concentration of free chlorine of at least 0.5 mg/litre after at least 30 min contact time at

[2] Including, for example, a residual concentration of free chlorine of ≥0.5 mg/litre after at least 30 min contact time at pH <8.0. WHO (2004) *Guidelines for Drinking Water Quality, Third Edition*, p 194; Geneva, World Health Organization Available at http://www.who.int/water_sanitation_health/dwq/gdwq3/en/index.html

[3] WHO Guidelines for Drinking Water Quality recommend bringing water to a rolling boil to assure adequate water disinfection.

pH <8.0. Where household water safety is suspect, authorities should consider advising families to treat their drinking water with available and acceptable household-level interventions, including home chlorination (addition of bleach) and boiling, that are effective at inactivating viruses.

What are the risks from recreational or other contact with water bodies contaminated by birds?

Potential modes of transmission of avian influenza virus to humans during recreational use of contaminated water include oral ingestion or aspiration of contaminated water as well as direct intranasal or conjunctival inoculation, however there is no evidence of this reported (*21*). The potential for exposure to the virus through recreational use of open bodies of water receiving significant waterfowl populations does exist and will increase with the number of birds and the time of year.

While the majority of human cases of H5N1 have been attributed to close contact with infected poultry or poultry faeces, the possibility of developing the disease following swimming or bathing in water with high loads of avian influenza virus has been suggested in two cases in Vietnam (*23*). Disease reportedly developed in a 35-year-old woman and an unrelated 9-year-old girl following swimming in water. The water in which the 35-year-old women bathed had reportedly been used for the disposal of dead poultry. However, it is not possible to conclusively attribute the infection to aspiration or ingestion of this potentially contaminated water, or to another type of exposure. Another potential case occurred in Cambodia where an 8-year-old female may have been exposed to the virus through recreational contact with contaminated water, where asymptomatic ducks may have shed virus into the pond. However, again, there is no evidence to confirm this hypothesis (Megge Miller, WHO Cambodia, pers comm).

Data on both exposure and effects assessment for avian influenza viruses in recreational exposures are lacking. Risk assessments for recreational exposure to other viruses may be useful as a model. For example, an assessment of adenoviruses in recreational water (24) modeled the risk of infection due to consumption during swimming.

Water bodies used for recreational purposes are almost never treated, and treatment may not be feasible. Authorities concerned can manage any potential risk from highly contaminated waters by advising the public of this risk, and, where a high degree or risk has been identified, by restricting human access to potentially hazardous sites.

What are the risks associated with sewage through inadequate domestic and workplace plumbing?

There is a precedent for the transmission of viruses from sewage to humans through interconnected sewage pipes and non-sealed venting (*19*). This was documented for SARS cases in the Amoy Garden complex in Hong Kong. The SARS virus was present in urine and faeces of infected humans and is stable for several days. There is some evidence to show that H5N1 is excreted in human faeces (*14*), and all influenza A viruses can be transmitted in the faeces of avian species.

Human and animal excreta are most often managed separately. However, as pointed out above, there are settings and scenarios where animal waste may be combined with human waste. If the sewage from poultry houses was mixed with human sewage, for example, there could be a risk of transmitting influenza through interconnected sewage pipes and non-sealed venting. In such situations, there need to be prevention and control measures to reduce airborne droplet and aerosol transmission. It is extremely poor design to have sewers vented through human living quarters, and such design defects should not be tolerated. Other means of excreta disposal such as latrines are likely to represent an extremely low risk because of the reduced likelihood of aerosol formation.

What are the risks associated with living or working near sewage treatment facilities or outfalls.

Assuming that humans have not become infected with avian influenza, and are not shedding avian influenza viruses in their excreta, there is little risk to sewage workers, providing poultry house discharge is not included with human sewage. In the event that humans have been infected with avian H5N1, human excreta could contain avian influenza viruses shed by humans, and the exposure risks to sewage workers would need to be reconsidered. In such a case, contaminated sewage should be treated to reduce virus numbers, and measures should be taken to reduce aerosol generation and exposure of individuals to aerosols (e.g., use of protective clothing, such as masks). As mentioned above, although there is no specific information available on the response of H5N1 virus to waste treatment processes, virus concentrations are generally reduced at various rates and to various extents in both human and animal waste treatment processes, but they are not completely eliminated (*18*). If the human sewage is mixed with animal waste, similar precautions would need to be taken.

Future research needs

There is a paucity of information on avian influenza H5N1 virus presence and stability in water and sewage, the site(s) of infection, its route of transmission from bird to humans through water and sewage and the associated risks to exposed humans.

Efforts to quantify avian influenza virus presence in water, sewage and related environmental media would be valuable and should be implemented soon for improved data to support decision-making. Additional data on the survival of the H5N1 virus in water and sewage under various environmental conditions would be useful for risk management.

Given the lack of information, efforts to better document and assess the risks from exposure to virus in water and sewage should be supported. Quantitative estimates of the range of influenza virus concentrations in bird faeces and in waters in which birds have congregated would provide better information on the potential viral loads that could be shed into the environment. From this, the virus concentration could be estimated based on dilution factors of faeces in water (such as a pond). These estimates could be compared with measured concentrations of the virus in surface waters. If this information was coupled with estimates of avian or mammalian infectivity (the dose–response relationship via oral ingestion or deposition in the upper or lower respiratory tract, as obtained from infectivity studies or by other means), further quantitative risk assessments for different exposure scenarios could be conducted.

More information is needed about the inactivation of avian influenza H5N1 viruses in water and in avian animal waste treatment and management processes and systems. Specifically, information on the effectiveness of disinfection and other treatment processes (e.g., chemical disinfectants, thermal and thermophilic treatment processes, UV radiation, drying and desiccation, pH, biological activity, etc.) and the virus's resistance to treatment would help to make estimates about extent of the risk from environmental wastes and sewage and about the efficacy of candidate prevention and control measures.

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Further Reading:

WHO Guidelines for drinking-water quality (available at http://www.who.int/water_sanitation_health/dwq/gdwq3/en/index.html).

WHO Guidelines for safe recreational waters Volume 1 - Coastal and fresh waters (available at http://www.who.int/water_sanitation_health/bathing/srwe1/en/).