Netherlands Food and Consumer Product Safety Authority
Ministry of Agriculture, Nature and Food Quality

> PO Box 43006 3540 AA Utrecht The Netherlands

To the Minister for Medical Care and Sport

Advice of the Director of the Office for Risk Assessment & Research

Concerning the public health risks associated with avian influenza virus in mechanically separated poultry meat

Office for Risk Assessment & Research

Catharijnesingel 59
3511 GG Utrecht
PO Box 43006
3540 AA Utrecht
The Netherlands
www.nvwa.nl

Contact

T +31 88 223 33 33
risicobeoordeling@nvwa.nl

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Background

On 25 November 2020 the Netherlands Food and Consumer Product Safety Authority (NVWA) received a notification from Wageningen Bioveterinary Research (WBVR) regarding a batch of mechanically separated chicken meat suspected of being contaminated with avian influenza virus. The batch had been supplied by a Dutch meat-processing plant. An examination of four samples provided by the company, conducted by WBVR at the company's own request, resulted in three of the four samples being tested positive in a PCR[1] test. Two of the PCR positive samples were then inoculated into incubated chicken eggs, after which virus could be isolated. This showed the presence of infectious virus in the samples provided. WBVR identified the virus as belonging to the HPAI H5N5 subtype. The batch of meat mechanically separated from deboned chicken carcasses was made up of meat from 11 European chicken-processing plants, nine of which were located in the United Kingdom, one in Germany and one in the Netherlands. The batch was produced on 23 November 2020.

Questions to be answered

The fact that the presence of an HPAI virus was demonstrated in a batch of mechanically separated meat intended for human consumption prompted the Dutch Ministry of Health, Welfare and Sport to present BuRO with the following questions:

1. *Can poultry meat infected with AI or HPAI virus pose a public health risk when humans consume or are exposed to such meat? Is there any difference, in this respect, between fresh poultry meat, meat preparations (in which mechanically separated meat is included) and meat products?*

2. *If so, what mitigating measures can be taken to sufficiently reduce this risk?*

Method

Given the fact that the Ministry's urgent questions required quick answers, BuRO performed a quickscan-type investigation. BuRO first sought to determine which HPAI viruses are currently going around in Europe. We then checked whether these viruses may constitute a public health hazard. Lastly, we elucidated whether

[1] Polymerase chain reaction, a rapid method used to multiply small amounts of genetic material.

the avian influenza viruses can be transmitted to humans through consumption of food.

For our literature review, we searched Scopus, using various combinations of the following search terms: H5, avian influenza, Europe, influenza, influenza A virus, route of infection, oral infection, food-borne, food safety, human, mammal. We also sought to find grey literature on Google.

Findings

Hazard identification
Due to the nature of the questions to be answered, BuRO's investigation focused solely on: AI and HPAI virus in poultry meat.

Hazard characterisation

Avian influenza viruses
Avian influenza viruses belong to the genus influenza A viruses of the Orthomyxoviridae family. They are viruses with single-stranded RNA and a segmented genome consisting of eight separate strands. Two surface glycoproteins, haemagglutinin (H) and neuraminidase (N), form the main antigens of the virus and are used to differentiate between the various subtypes (e.g. H5N8).(Nelson & Vincent, 2015) All influenza A viruses, even those circulating in mammals, ultimately hail from birds.(Webster, 1998) Depending on how likely they are to cause illness in chickens, avian influenza viruses are categorised as lowly pathogenic (LPAI) AI strains (which generally cause few or no clinical symptoms) and highly pathogenic AI (HPAI) strains (which may present with severe morbidity and high mortality rates).

One of the characteristics of avian influenza and other influenza viruses is that new subtypes emerge quite regularly. This is due to an error-prone RNA polymerase and the segmented genomes. If two different influenza A viruses infect one single cell, the exchange between one or more genome segments between the viruses (reassortment) may result in an abrupt change of the viral progeny. This is called the antigenic shift. It may result in the genesis of viruses with a new haemagglutinin (H) and/or a new neuraminidase (N). In addition, viruses can mutate in a more gradual way: the RNA polymerase lacks proofreading and post-replication repair mechanisms that result in a gradual accumulation of point mutations during replication. This is called antigenic drift.(Munoz et al., 2016)

In addition to the regular emergence of new subtypes, influenza A viruses are characterised by their ability to infect new hosts. Their host range is comprehensive. In addition to water birds, it includes poultry, pigs, humans, dogs, cats, whales, seals and various other types of mammals. (Short et al., 2015). In mammals, incidental transmission of influenza A viruses that originated in wild or domesticated birds may occasionally result in infection, self-limiting epidemics or, in rare cases, persistent transmission that may result in recurring epidemics involving mutated variants. The latter has happened in humans, pigs, horses and dogs, in which specific strains of a limited number of subtypes have become endemic.(Reperant et al., 2012) However, stable transmission in a new type of host is a rare occurrence.(Nelson & Vincent, 2015) Virus transmission is inhibited by various factors, including congenital immunity and the receptor preference of influenza A viruses. On the other hand, there are intracellular factors and virus

mutations that facilitate virus replication and transmission to a new host, and so help viruses overcome these barriers.(Parrish et al., 2015)

Although influenza A viruses are characterised by their ability to infect new hosts, this does not happen very often. Zoonotic (avian) influenza viruses may be transmitted to humans from time to time, typically without further human-to-human transmission. In order to successfully adapt to human hosts, zoonotic influenza viruses must overcome three barriers: animal-to-human transmission barriers, virus-host cell interaction barriers and human-to-human transmission barriers. Human-to-human transmission barriers appear to represent a major obstacle for zoonotic influenza viruses..(Reperant et al., 2012) If a zoonotic influenza virus develops the ability to be transmitted from human to human, a pandemic may ensue in rare cases.(Nelson & Vincent, 2015)

Human infections with avian influenza viruses

Direct and indirect exposure to infected poultry (dead or alive) or to a contaminated environment (e.g. bird markets) is considered the main risk factor for human infection with an avian influenza virus. The slaughter, plucking and handling of the carcasses of infected poultry and preparation of the meat in a domestic setting probably constitute risk factors, as well.(Harder et al., 2016; WHO, 2018) The vast majority of all known human infections with avian influenza viruses were infections with HPAI H5N1 and LPAI H7N9 viruses. In addition, a few cases of infection with avian influenza viruses of subtypes H6, H9 and H10 have been reported.(Harder et al., 2016) Between 2003 and October 2020, the WHO received 861 notifications of confirmed human H5N1 cases , of whom 455 deceased. Most cases were reported in Egypt (359) and Indonesia (200).(WHO, 2020). In addition, between 2013 and August 2018, the WHO was notified of 1,567 confirmed cases of H7N9 infection, with at least 615 mortalities. Apart from three cases, all infections occurred in China.(WHO, 2020)

H5 avian influenza viruses in Europe in the autumn of 2020

In 2020, EFSA (2020) published an update on the avian influenza situation in Europa. Since 16 October 2020 several European countries, including Belgium, Denmark, France, Germany, Ireland, Sweden, the Netherlands and the United Kingdom, have reported outbreaks of HPAI viruses. Until 19 November 2020, the presence of H5-type HPAI viruses had been demonstrated 302 times, mostly in wild birds (281 times), but also to a significantly lesser extent in poultry (18) and kept birds (3). The HPAI viruses identified belonged to the H5N8, H5N5 and H5N1 subtypes. All three viruses developed from one common predecessor that underwent multiple reassortment events. In the 302 samples tested positive, H5N8 was by far the most common subtype (present in 284 samples). The H5N5 and H5N1 viruses were demonstrated five and four times, respectively. With regard to the remaining viruses, either the N type or both the N and H types were unknown in 8 and 1 cases, respectively. As for poultry, the majority of the samples tested positive (16 out of 18) also involved the H5N8 virus.(European Food Safety Authority et al., 2020) It should be noted that the H5N1 virus that is currently circulating in Europe is not related to the H5N1 virus that has been transmitted to humans in Southeast Asia since 2003.(European Food Safety Authority et al., 2020)

Human infections with currently circulating H5-type HPAI viruses

The virus that was detected in the mechanically separated meat was identified as HPAI H5N5. The genome segments of this virus are identical to those of H5N8,

except for the N5 segment, which was obtained by reassortment (personal communication from Marc Engelsma). According to EFSA, no human infections with H5N5 and the two other H5-type HPAI viruses currently circulating in Europe have been demonstrated so far. Nor have these viruses been found to contain sequences associated with adaptation to mammal hosts, which would pose an increased risk of animal-to-human transmission.(European Food Safety Authority et al., 2020) EFSA has indicated that the risk of any of the currently circulating HPAI viruses being transmitted to the population at large is very small. Given the low zoonotic potential of these viruses and the control measures governing poultry holdings laid down in EU regulations, the risk of virus transmission to humans through potentially infected poultry products is deemed negligible.(European Food Safety Authority et al., 2020) According to the WHO, the probability of humans being infected with the H5N8 HPAI virus are slim, but cannot be entirely ruled out.(WHO, 2016) No indication of human infections were found in three (sero)epidemiological studies among almost 9000 persons involved in H5N8 related cullings or small scale poultry farmers.(Adlhoch et al., 2018; Olsen et al., 2019; Gomaa et al., 2020)

Exposure and risk assessment

Human infection with avian influenza viruses through consumption of or exposure to infected meat

Unlike LPAI variants, HPAI viruses cause systemic infections in infected poultry. As a result, high viral loads may be found in internal organs and muscle tissue.(Harder et al., 2016) These viral loads are high enough to infect and cause symptoms in predators such as felines and martens.(Harder et al., 2016) There are no signs that avian influenza viruses can be transmitted to humans through consumption of properly heated poultry meat.(Harder et al., 2016; WHO, 2018) 'Properly heated' means heating to 70ºC or more for several seconds, resulting in complete inactivation of virus particles.(Harder et al., 2016) However, there is scant evidence that humans might be infected with HPAI H5N1 virus through consumption of insufficiently heated poultry products. In infected persons whose only initial symptom was diarrhoea, it was found that the only plausible way in which they could have been exposed to poultry was the consumption of a meal that included raw duck's blood.(Gambotto et al., 2008) It is unusual for poultry meat to be consumed raw in Europe. Therefore, it seems unlikely that humans will be exposed to avian influenza viruses in this way.(European Food Safety Authority et al., 2018)

Due to the potential presence of virus in meat, exposure to meat obtained from poultry infected with HPAI viruses constitutes a potential route for human infection.(Harder et al., 2016) When poultry is infected with LPAI virus variants, symptoms are generally found in the respiratory and digestive systems. Therefore, infectivity will be much lower in muscle tissue.(Harder et al., 2016)

Regulation (EC) No. 853/2004 defines meat preparations as *fresh meat [...], which has had foodstuffs, seasonings or additives added to it or which has undergone processes insufficient to modify the internal muscle fibre structure of the meat and thus to eliminate the characteristics of fresh meat.* Meat products are defined as *processed products resulting from the processing of meat or from the further processing of such processed products, so that the cut surface shows that the product no longer has the characteristics of fresh meat.* In other words, meat preparations contain raw meat, while meat products contain cooked meat. This being the case, in principle, infectious virus may still be present in meat

preparations, but it is unlikely to be present in meat products, provided that they have been heated to a sufficient temperature. In other words, the risk posed by the presence of avian influenza virus in meat preparations intended for human consumption is pretty much identical to the risk posed by fresh meat.

Risk assessment

Unlike the small-scale poultry farms found particularly in many parts of the developing world, poultry farms in Europe are highly professionalised and industrialised, and live poultry markets have become virtually non-existent here. Therefore, consumers in this part of the world are very unlikely these days to be exposed to the main routes of transmission to avian influenza virus, e.g. direct exposure to living poultry. Moreover, regulations are in place in Europe, laid down in Council Directive 2005/94/EC on community measures for the control of avian influenza, to ensure that avian influenza monitoring is in place and that, when infections are detected, measures are taken to prevent meat obtained from infected poultry from reaching consumers. Moreover, poultry infected with an HPAI virus presents with severe symptoms and high mortality rates, making it unlikely that such animals will be slaughtered for consumption. However, a scenario might unfold in which the very recent introduction of an HPAI virus in a flock has not yet resulted in many birds developing symptoms and has therefore gone unnoticed. When such birds are transported to a slaughterhouse, it is not inconceivable that some infected birds might end up in the food chain. This may go some way towards explaining why HPAI virus was present in the batch of mechanically separated meat under discussion. However, it seems highly unlikely that such a scenario will unfold. Therefore, judging from the information available at present, we believe that it was an exceptional coincidence that AI virus was found in a batch of mechanically separated meat. All things considered, it is highly unlikely that meat obtained from HPAI-infected poultry will end up in the food chain. However, in the unlikely event that it does end up in the food chain, compliance with proper kitchen hygiene rules will render the risk posed to public health negligible. By 'proper kitchen hygiene rules' we are referring to the hygienic domestic preparation of poultry meat in such a way as to prevent infection with *Campylobacter* or *Salmonella*, as recommended by the government and the Netherlands Nutrition Centre, thus, for example, preventing hand-to-mouth contact from resulting in avian influenza infection. In addition, poultry meat is generally cooked well before consumption in Europe, thus eliminating any virus which may be present in the meat. Lastly, there are biological barriers, such as the availability of the right cell receptors to which avian influenza viruses must bind in order to be able to enter a cell.(Reperant et al., 2012) These barriers prevent avian influenza viruses from being easily transmitted to humans. In summary, the probability of HPAI influenza viruses being present in poultry meat is very slim, and the resulting risk to consumers is deemed to be very slim to negligible.

Conclusion and answers to the questions

Conclusion

It is highly unlikely in Europe that poultry meat infected with HPAI avian influenza virus will end up in the food chain. The presence of biological barriers, maintaining proper kitchen hygiene and cooking or heating of poultry meat prior to consumption render the probability that this leads to of infection of consumers negligible.

Answers to the questions raised by the Ministry of Health

1. *Can poultry meat infected with AI or HPAI virus pose a public health risk when humans consume or are exposed to such meat? Is there any difference, in this respect, between fresh poultry meat, meat preparations (in which mechanically separated meat is included) and meat products?*

The demonstration of infectious HPAI virus in in a batch of mechanically separated chicken meat has to be regarded as an exceptional coincidence. The a priori probability of (HP)AI virus being present in poultry meat in the Dutch consumer market is very slight. In the European context, the public health hazard associated with the consumption of, or exposure to, poultry meat infected with infectious virus is currently deemed to be very small to negligible. There is no real risk disparity between fresh poultry meat and meat preparations containing mechanically separated meat. When meat products are properly heated, consumers are not exposed to AI or HPAI virus.

2. *If so, what mitigating measures can be taken to sufficiently reduce this risk?*

Other than the standard recommendations regarding proper kitchen hygiene in the processing of poultry meat, the preparation of poultry meat and proper heating of poultry meat or poultry meat products, no additional mitigating measures are required,

Advice

Advice to the Minister for Medical Care and Sport
Bring this opinion to the attention of the Netherlands Nutrition Centre. Request the Netherlands Nutrition Centre to consider the opinion in the information provided to the general public regarding the importance of proper kitchen hygiene and proper heating of poultry meat when preparing it for consumption.

Yours sincerely,

Office for Risk Assessment & Research
Prof. Antoon Opperhuizen

Addendum dated March 3d, 2021

Office for Risk Assessment & Research

Date
4 February 2021

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Cause
The advice of the director BuRO concerning the public health risks associated with avian influenza virus in mechanically separated poultry meat is based on knowledge that has been available on November 30th, 2020. At that time, human infections with H5N8 avian influenza virus were not known. On February 18th, 2021, however, Russian authorities notified WHO of the detection of H5N8 virus in clinical specimens from seven persons. These are the first ever reported infections of H5N8 in humans. All persons were involved in H5N8 related culling activities on a 900,000 animal laying hen farm. Samples were taken at the time of culling between December 11th and 18th, 2020 and thereafter in the course of surveillance activities among poultry workers. None of the persons tested positive, displayed symptoms (WHO, 2021).

ECDC assessment
The detection of human H5N8 infections in Russia prompted the European Centre for Disease Control (ECDC) to perform a brief threat assessment. ECDC assesses the infection risk of H5N8 avian influenza virus for the general public still to be very low and that of poultry workers to be low. As the assessment is based on limited data, ECDC notes that there is considerable uncertainty regarding the conclusions reached (ECDC, 2021).

Significance of the recent developments for the advice of the director of BuRO
The reasoning of the advice remains unchanged for the most part:

- In Europe, consumers are very unlikely to be exposed to avian influenza virus through the most important transmission routes, that is direct exposure to living poultry.
- Statutory surveillance and control measures prevent meat of infected poultry from entering the food chain.
- Proper kitchen hygiene and sufficient heating of poultry meat prevent exposure of consumers to avian influenza virus.

The recent detection of human infections with H5N8 avian influenza virus weakens the argument of the existence of biological barriers. However, H5N8 remains avian adapted without genetic markers for mammalian adaptation (ECDC, 2021).

For the time being, the tenor of the advice of the director of BuRO remains unchanged.

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