



## H7N7 Dutch Avian Flu Outbreak (2003) Associated with Human Conjunctivitis and Fatal Case of Acute Respiratory Distress Syndrome in Exposed Veterinarian Who Did Not Take Tamiflu or Receive Vaccination

**Biot #345:** April 02, 2006

At about the same time the SARS novel virus outbreak was swirling in Canada and the Far East (March-June 2003), a highly lethal disease subsequently identified as avian influenza virus subtype H7N7 was devastating commercial chicken flocks on (initially) six farms in Gelderland Province, the Netherlands, an area with a high density of poultry farms. Eventually the infection spread to 255 farms, and on March 1, 2003 the Dutch Ministry of Agriculture announced a ban on the export of all poultry and poultry-related products. In addition, the Ministry ordered the culling of all infected flocks, which led to the killing of around 30 million chickens—about 28% of the total chicken population in the Netherlands. The human population in the Netherlands is 16 million people.



Map showing Gelderland Province (in red) in The Netherlands. Source: [http://www.aisr.cistron.nl/online\\_curriculum/holland\\_online/province\\_activity\\_Pages/gelderland/gelderland.html](http://www.aisr.cistron.nl/online_curriculum/holland_online/province_activity_Pages/gelderland/gelderland.html); accessed April 2, 2006.



Obtaining a swab for diagnosing disease from a presumably sick chicken. Source: [http://www.avian-influenza.com/Disease/Avian\\_poultry/Diagnosis.asp](http://www.avian-influenza.com/Disease/Avian_poultry/Diagnosis.asp); accessed April 2, 2006.

### Assumed Low Risk of Avian Virus Transmission to Humans Quickly Proved False

At first the risk of transmission of the virus to humans was thought to be low, but almost immediately in early March 2003, reports of H7N7-associated eye infections began surfacing. The first confirmed case of H7N7 conjunctivitis came from a veterinarian who had visited several farms with infected flocks (more on him below). Occasional case reports of H7N7-associated conjunctivitis had been previously reported in the scientific and medical literature, including one report in 1996 that isolated the H7N7 virus from a 43-year-old duck owner with conjunctivitis. (1-4)



Diagram of eye showing normal conjunctiva (left) and inflamed conjunctiva, as in conjunctivitis (right). Source: <http://www.doctorworks.net/patientedillustrated.htm>; accessed April 2, 2006.

Conjunctivitis is inflammation of the membrane on the inner part of the eyelids and the membrane covering the white of the eye. The conjunctival membranes react to a wide range of bacteria, viruses, allergy-provoking agents, irritants and toxic agents. Other common names for conjunctivitis are “pinkeye” and “red eye”.

Coincidentally, data from routine influenza virus surveillance suggested a late seasonal

increase in the rate of human influenza viruses. The combination of an avian influenza

outbreak and a potential human influenza outbreak suggested the perfect setting for

mixing of genes within persons sick with both viruses (avian and human influenza viruses) at the same time. Dutch health authorities were on edge, especially when TWO different veterinarians involved in control measures for the highly pathogenic avian influenza (HPAI) epizootic tested positive for H7N7-confirmed conjunctivitis AND human influenza virus A (subtype H3N2). (4) An epizootic is a disease that is only present in an animal population for limited periods, but has a high morbidity rate.



Rijksinstituut voor Volksgezondheid and Milieu or RIVM (National Institute of Public Health and Environment) in the Netherlands. Source: <http://www.rivm.nl/over-rivm/>; accessed April 2, 2006.

Dutch health authorities requested that all workers in poultry farms, poultry farmers, and their families report signs of conjunctivitis or influenza-like illness. People who came forward with these complaints were then tested for influenza virus type A subtype H7 infection and also completed a questionnaire about their type of symptoms, duration of illness, and possible exposures to infected poultry. (5)

The Dutch health authorities received complaints from 453 people. Of the 453, 349 (77%) reported conjunctivitis, 90 (20%) had influenza-like illness, and 67 (15%) had other complaints. Of the persons complaining of conjunctivitis only, the H7N7 avian flu virus was detected in 78 (26%) of conjunctival samples. In persons who complained of conjunctivitis AND influenza-like illness, H7N7 avian flu virus was detected in 5 (9%) of conjunctival samples.

In persons who complained of influenza-illness only, conjunctival swabs from 2 (5%) of them tested positive for H7N7. (5) Indeed, of the 2 primary A/H7 cases with influenza-like illness only, one had a previous eye injury, precluding evaluation for conjunctivitis, and the other was a veterinarian with chronic blepharitis who developed a respiratory distress syndrome and died (more on him below). Blepharitis is inflammation of the eyelids.

Most positive samples had been collected within the five days of symptom onset in affected persons. Six (6) persons had evidence of coexisting human influenza A H3N2 infection, as diagnosed from nose/throat swabs taken at the same time as conjunctival swabbing, for which patients gave written consent. The health authorities developed careful case definitions for conjunctivitis and influenza-like illness, which are available in the Koopmans *Lancet* article. (5)

### **Control Measures Implemented**

On March 3, 2003, following confirmation that A/H7N7 WAS the cause of the avian influenza outbreak, the outbreak management team advised all workers who screened and culled poultry to wear protective eye glasses and mouth and nose masks to reduce contact with avian influenza virus. People with symptoms of influenza-like illness were told to stay home. When the first case of A/H7-confirmed conjunctivitis was diagnosed on March 7, 2003, and in view of the increase in the number of influenza virus cases, on March 9, 2003, the outbreak management team recommended mandatory vaccination with INACTIVATED INFLUENZA VIRUS vaccine be offered to all poultry workers who handled, screened, or culled potentially infected chickens. The point of this vaccination was to reduce the risk of a possible genetic mixing or reassortment of avian and human influenza virus in one person through prevention of infection with human influenza virus.

Within one day, all workers had been convinced to be vaccinated, according to Koopmans. On March 14, 2003, when 19 cases of A/H7 had been confirmed, as well as the first confirmed case of transmission of the disease from one human to another (see more below), preventive measures were “stepped up.” Authorities emphasized the need for personal protection and the good hand hygiene after leaving the workplace. Treatment with oseltamivir was recommended for all new conjunctivitis cases, and a prophylactic regimen of oseltamivir (75 mg daily) was recommended for all people handling potentially infected poultry, and was supposed to be continued for 2 days after their last exposure to the infected chickens. The recommendation for vaccination was extended to all poultry farmers and their families in a 2 mile radius of infected poultry farms, and those suspected of having the infection. More than 4000 people were vaccinated between March 11 and April 2, 2003. Oseltamivir prophylaxis was allegedly also provided to about 2500 exposed workers and more than 600 farmers and family members. (10)

More than half (56%) of influenza A/H7 infections reported to the Dutch authorities arose before the vaccination and treatment program.



Paris chicken barns. Source: [http://asms.k12.ar.us/armem/virtual\\_tour2002/RebeccaSmith/Disk%203/Mvc-201f.jpg](http://asms.k12.ar.us/armem/virtual_tour2002/RebeccaSmith/Disk%203/Mvc-201f.jpg), accessed April 2, 2006.



Another photo of chicken barns near Paris. Source: [http://asms.k12.ar.us/armem/virtual\\_tour2002/RebeccaSmith/Disk%203/Mvc-202f.jpg](http://asms.k12.ar.us/armem/virtual_tour2002/RebeccaSmith/Disk%203/Mvc-202f.jpg), accessed April 2, 2006.

On Friday April 4, 2003, the outbreak of A/H7 in chickens expanded to two different regions of the Netherlands (North Brabant and Limburg). Authorities determined that the spread probably occurred when at least eight people working in Gelderland returned home to North Brabant and Limburg where they lived. Veterinary control of the outbreak “highlighted the importance of movement restrictions for animals, vehicles, and human beings, but several breaches of practice were detected,” according to Koopmans. (8)

### Mean Age of Infected Persons

The mean age of people in a case register kept by the Health Ministry was 32.8 years (standard deviation large at 16.4 years, the range in age was 0 to 103 years!). In confirmed A/H7 cases the average age was slightly lower at 30.4 years (standard deviation again large at 12.3, range in age 13 to 59 years). The peak incidence was between March 8, and March 20, 2003. The attack rate (proportions of persons at risk who developed symptoms) of conjunctivitis was highest in veterinarians, but cullers and veterinarians had the highest estimated attack rate of confirmed A/H7 infections. (6)

### Sick Veterinarians

On March 5, 2003, one previously healthy veterinarian developed acute conjunctivitis after visiting several farms with HPAI-infected poultry flocks. The symptoms in the first eye started 30 hours after his last farm visit. Within 24 hours, the second eye became infected. Eye swabs were collected from the veterinarian 30 hours after symptom onset (60 hours after the farm visit), and these swabs were positive for influenza A/H7 by both PCR (Polymerase Chain Reaction) and tissue culture. On the basis of these results, the Dutch health authorities began active case finding (not simply waiting for sick people to report themselves to authorities) on March 10, 2003.

The second veterinarian—the one mentioned earlier with chronic blepharitis—was a previously healthy 57-year old. However, on April 4, two days after visiting a farm with infected chickens in Teeffelen, the Netherlands, for just a few hours, he developed a high fever and severe headache WITHOUT cough, difficulty breathing or other respiratory signs, and WITHOUT eye problems other than his chronic blepharitis noted earlier. When he first visited his family doctor for persisting fever and headache 4 days later (April 8, 2003) (6 days after visiting the farm), his family doctor noted NO signs of respiratory disease or conjunctivitis, so no medications (no Tamiflu) were prescribed and no vaccination was

administered. However, the next day, on April 9, 2003, throat and eye swabs were collected from the sick veterinarian. Tests on these were subsequently negative both for the avian influenza virus and for a range of other respiratory pathogens.

On April 11, 2003, nine days after the veterinarian visited the chicken farm, he was (finally) admitted to a hospital in Hertogenbosch, The Netherlands, with pneumonia. "His condition deteriorated despite treatment with antibiotics, he developed multi-organ failure. On day 15 [April 17, 2003], he died of respiratory insufficiency. A broncho-alveolar lavage sample collected on day 11, and lung tissue taken during autopsy tested positive for A/H7 with PCF and cell culture [laboratory methods]. Histopathology of the lung tissue showed extensive diffuse alveolar damage" consistent with acute respiratory distress syndrome. (6) A full description of his dramatic clinical course is available in **Ron A. M. Fouchier's article listed as #13 in sources at conclusion of this Biot.**

### **Human-to-Human Transmission?**

Dutch health authorities reported evidence of H7N7 influenza from 2 poultry workers to 3 family workers who themselves had no direct exposure to infected flocks. All 3 family members had H7N7-confirmed conjunctivitis and one also had influenza-like illness. This occurrence seemed to suggest person-to-person transmission of a novel pandemic influenza virus strain that has managed to fully adapt itself to live and replicate in humans. A prerequisite for this to take place is simultaneous infection of a susceptible host, which can be a pig or a human, with both avian and human influenza viruses, resulting in viral offspring that have a mixture of the genome segments derived from both parental strains. (7-8)



Inside a chicken barn in New Zealand. Source: <http://home.xtra.co.nz/hosts/Bunkle/images/P0000989.jpg> and [http://home.xtra.co.nz/hosts/Bunkle/news\\_chickens.htm](http://home.xtra.co.nz/hosts/Bunkle/news_chickens.htm), accessed April 2, 2006.

### **Resistance to Advocating Use of Oseltamivir (Tamiflu) by Dutch Health Planners?**

Koopmans, et al, reported that "health planners" had reservations about the widespread and lengthy use of oseltamivir by humans for prophylaxis during March and early-mid April 2003 as the epizootic ran its course. (9) When the massively H7N7-infected veterinarian died on April 17, 2003, the health planners saw the light, and so did workers whose use of Tamiflu suddenly increased.

The arguments of health planners against initially using oseltamivir, according to the Koopmans article, were (the ordering is as listed by Koopmans):

1. "The ethical dilemma of prescribing a drug with possible side effects to healthy people so as to protect others." [Indeed, "although side effects from oseltamivir are not common, they can occur", says Medline Plus (11). The possible symptoms are: "upset stomach, vomiting, difficulty sleeping, bronchitis, and dizziness."]
2. "Mass prescription of drugs without individual medical guidance could negatively affect the national policy of restricted drug use."
3. "Potential for development of resistance."
4. "Implementation and improvement of personal protection measures might be as effective as drug treatment."
5. The rate of nonadherence to oseltamivir might be as high as that for personal protection. At first, people were slow to accept antiviral medication; however, the uptake rate increased after the fatal case." (9)

## The World Health Organization Gets Involved

As a consequence of the work performed by Fouchier, et al. (13) in the Netherlands, the World Health Organization Global Influenza Surveillance Network initiated the development of test kits and candidate vaccines, according to Fouchier. Fouchier noted in closing: "In accordance with the World Health Organization pandemic preparedness plan, surveillance and diagnosis should be enhanced in humans and in susceptible animals in countries where cases of H7N7 infection are detected."

### Summary

The size of the H7N7 avian flu outbreak in the Netherlands in 2003 was very large and coincided with peak activity of human influenza virus. This confluence of events created fertile ground for mixing of genes from aviana and human viruses in humans (or pigs), which did not occur, to the best of anyone's knowledge. By the time the epidemiology was completed in a week after confirmation of the first case of human infection on March 3, 2003, the "sobering conclusion" reached by Koopsman, et al, was that "more than 1000 people from all over the Netherlands and from abroad had [already] been exposed." (12) He continued: "Therefore, if a variant with more effective spreading capabilities had arisen, containment would have been very difficult." (12)

As a result of the experience of the 2003 H7N7 outbreak experience in the Netherlands, the World Health Organization strongly suggests that any time cases of H7N7 infection are detected in a country, that country must enhance its pandemic preparedness plan, surveillance, and diagnosis in humans and in susceptible animals (e.g., pigs, birds, seals). (13).

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