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Original Articles

Outbreak report

Human-to-human transmission of avian influenza A/H7N7, The Netherlands, 2003

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An outbreak of highly pathogenic avian influenza A virus subtype H7N7 began in poultry farms in the Netherlands in 2003. Virus infection was detected by RT-PCR in 86 poultry workers and three household contacts of PCR-positive poultry workers, mainly associated with conjunctivitis. To determine the magnitude of and risk factors for human-to-human transmission of influenza A/H7N7 in the Netherlands, a retrospective cohort study among household members of infected poultry workers was undertaken. In total, 33 (58.9%) of 56 (among 62) participants who provided blood samples had positive H7 serology, using single convalescent serum samples obtained at least 3 weeks after onset of symptoms of the index case. Eight household members (12.9%) reported symptoms (conjunctivitis and/or ILI), of which four of five (80.0%) tested seropositive. On univariate analysis, significant risk factors for seropositivity included having at least two toilets, a pet bird, and using cloth handkerchiefs. It was not possible to obtain a stable model for binomial regression for the outcome of A/H7N7 infection. Further seroprevalence studies among contacts of asymptomatic H7 cases should be conducted.

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Background

On 28 February 2003, the highly pathogenic avian influenza A virus subtype H7N7 (HPAI A/H7N7) was isolated for the first time in the Netherlands from poultry on a farm, identifying the start of

a large epizootic that also affected Germany and Belgium. In the Netherlands, infected poultry on 255 farms were culled, as well as poultry on 1094 surrounding farms, resulting in the killing of more than 30 million chickens [1]. Hygienic measures, and application of personal protective equipment and antiviral prophylaxis were advised. The following weeks, A/H7N7 was diagnosed by RT-PCR in 89 humans, of whom 78 had conjunctivitis. A Dutch veterinarian reported having conjunctivitis, which developed one day after he had visited an affected farm, and he died a week later from respiratory distress [2]. Three of the 89 cases were household contacts of A/H7N7 confirmed cases and had no known exposure to A/H7N7 infected poultry. This strongly suggested human-to-human transmission, either direct or indirect. All three patients had conjunctivitis, and one also had influenza-like illness (ILI).

Influenza in humans and HPAI is caused by influenza A virus, belonging to the family *Orthomyxoviridae*. All currently known influenza A virus subtypes have been found to circulate in waterfowl [3,4]. Avian influenza viruses have been known to infect humans, but transmission between humans has so far only occurred sporadically [5,6,7]. Influenza A/H7N7 in humans was first reported in 1959 [8]. In January 2004, human cases of influenza A/H5N1 related to an outbreak of avian influenza A/H5N1 were identified in Vietnam and Thailand [9] and in September 2004, probable human-to-human transmission was reported in a family cluster in Thailand [10].

Simultaneous infection of a susceptible host with a human and an animal influenza A virus could lead to re-assortment of genetic material and consequently cause the generation of a virus subtype capable of replicating and spreading between humans and with surface proteins that are novel for the human population (antigenic shift). Such strains could cause a major influenza pandemic

In order to measure secondary transmission of avian influenza A/H7N7 in household members, to identify risk factors for transmission, and to describe the clinical course of illness, we conducted a retrospective cohort study among household members of infected poultry workers.

Methods

Patients who were A/H7N7 confirmed index cases were contacted by telephone for recruitment of their household members in the study. People living on poultry farms or those who kept poultry in their gardens (backyards) were excluded from the study.

Definitions

An A/H7N7 confirmed index case was a person who had conjunctivitis and/or ILI, who had been exposed to influenza A/H7N7 infected poultry since 28 February 2003 in the Netherlands, and who had positive influenza A/H7N7 laboratory results by PCR and/or virus isolation.

Conjunctivitis - a possible case of A/H7N7 conjunctivitis was a household member with no known exposure to poultry and with two or more of the following symptoms since 28 February 2003: red eyes, tearful eyes, itching eyes, painful eyes, burning eyes, purulent fluid in eyes, or sensitivity to light. A confirmed case of A/H7N7 conjunctivitis was a possible case of A/H7N7 conjunctivitis with positive influenza A/H7N7 laboratory results by PCR and/or virus-isolation.

Influenza-like illness - a possible case of A/H7N7 influenza was a household member with no known exposure to poultry and with fever (if measured, then ≥ 38.5°C), and at least one of the following symptoms since 28 February 2003: cough, rinorrhoea, sore throat, myalgia, or headache. A confirmed case of A/H7N7 influenza was a possible case with positive influenza A/H7N7 laboratory results by PCR and/or virus-isolation.

Seropositive – a serology confirmed case of A/H7N7 infection (symptomatic or asymptomatic) was a household member who had an antibody titre of 1:10 or higher for influenza A/H7N7 by haemagglutination assay [11].

Questionnaire

Information on demographics, occupation, smoking, medical history, pets, contact with A/H7N7 confirmed index cases (including hygienic measures by index cases and contacts), exposure to A/H7N7-infected poultry, influenza vaccination status, and symptoms since 1 March 2003 were collected using a standardised, self-administered, postal questionnaire.

Serology

All participants were asked to provide single serum samples, at least 3 weeks after diagnosis of the primary A/H7N7 case in their household, to ascertain (sub)clinical infection with influenza A/H7N7. Sera were tested in a modified haemagglutination inhibition as described in detail by Meijer et al [11].

Ethical clearance for the study was obtained from the Dutch Medical Ethics Committee.

Statistical analysis

Data were analysed with STATA 8.0. For multivariate analysis of significant or biologically plausible variables in univariate analysis we preferred binomial to logistic regression because of high prevalence of positive A/H7N7 serology in household members in this cohort study, which calls for adjusted risk ratio's rather than odd rations. Fisher's exact test was used to calculate significance.

Results

Description of study participants

Of 86 households of A/H7N7 infected poultry workers, 63 (73.3%) households agreed to participate and 14 declined. Nine poultry workers could not be reached, of which four were immigrant workers that had returned to their home country Poland. Of the 200 household members in the 63 participating households, 104 (52%) completed and returned the questionnaire.

Of these 104, 42 were excluded, as they had either been exposed to H7N7-infected poultry, or were family members who were not living at the same address as the index case. A total of 62 household members of 25 A/H7N7 confirmed index cases were included in the study, with one single A/H7N7 confirmed index case in each of these households.

The male:female ratio was 2:3. Mean age was 27.3 years, ranging from 0 to 61 years. The mean household size was 3.5 people (range 2 – 8).

Clinical symptoms

Eight people (12.9%) reported health complaints. Two met the case definition of conjunctivitis only, four met the case definition of ILI only and two met both case definitions. In table 1, the risk factors for conjunctivitis among household members are summarised. Attack rates were higher in those who had allergies in their medical history than in those who did not (RR = 10.3, 95% confidence interval 1.2 – 91.0).

TABLE 1

Risk factors for conjunctivitis among household members of influenza A/H7N7-infected persons, N = 62 (univariate analysis), The Netherlands, 2003

	Total no. of persons	No. of cases	RR	95% CI	P value*
Allergy in medical history	14	3	10.3	1.2-91.0	<0.05
Sharing a washcloth	8	2	5.9	0.96-35.9	0.097
Sharing a towel	12	2	4.2	0.07-26.7	0.17
Use of cloth handkerchief	22	3	5.5	0.6-49.4	0.12
Smoking	5	1	3.8	0.05-30.1	0.29
Index: good hygiene	43	4	U†	-	0.57
Pet bird inside home	9	1	2.0	0.2-16.9	0.48
Other pets living inside home	37	3	2.0	0.2-18.4	0.64

* P value using Fisher's exact test

† U= undetermined

Results serology

In total, 56 of the 62 people in the cohort agreed to provide blood samples, of which 33 (58.9%) had detectable antibodies against H7. Five of eight household members with health complaints were serologically tested; four (80.0%) had detectable antibodies against H7, of which two had conjunctivitis only with onset two to six days after onset of symptoms in the index case, and two had conjunctivitis as well as symptoms of ILI with onset unknown or 5 days after onset of symptoms in the index case. Out of 24 households serologically tested, 15 (62.5%) had one or more household contacts with detectable H7 antibodies [Table 2].

A/H7 seroprevalence in household members was higher among those who had pet birds (e.g., canary) kept indoors at home and among those having any other indoor pets in their homes (e.g., cat, dog, hamster) than among those who did not [Table 3]. Furthermore, seroprevalence was higher among those who frequently used cloth handkerchiefs than among those who did not. Conversely, those who used paper handkerchief had a lower seroprevalence of H7 antibodies than those who did not. Seroprevalence was higher among those who had at least two toilets in their homes, than among those who had only one toilet. At household level, seroprevalence was higher among the 17 households that had two or more toilets in the home than among the 7 households with only one toilet at home (RR = 2.7, 95% confidence interval 0.8-8.9, p = .061).

Family members of index patients who had their first poultry exposure on or after 5 March 2003 had lower seroprevalence, showing borderline significance, than household members of index cases with first poultry contact before 5 March.

Two (3.2%) of 62 persons received the 2002-2003 influenza vaccination.

It was not possible to develop a stable model of significant and biologically plausible risk factors in univariate analysis for binomial regression.

The HI assay had a sensitivity of 85% and a specificity of 100% at a cut-off HI titre of ≥10. HI antibodies against influenza A/H7, A/H1, and A/H3 were not cross-reactive with the heterologeous virus. None of the human sera tested showed neutralisation of the A/H7N7 virus in the microneutralisation assay.

Discussion

We describe the occurrence of infection with avian influenza A virus subtype H7N7 in household contacts of human A/H7N7 confirmed index cases, in the absence of contact with infected poultry. Thirty three of 56 household members (58.9%) had an A/H7N7

Table 2

Seroprevalence of H7-antibodies among household contacts by number of susceptibles (n=56) within the household, The Netherlands, 2003

Number of susceptibles per household	Number of households	Total number of susceptibles	Number of contacts with H7-antibodies	Prevalence (%)
1	12	12	4	33%
2	1	2	2	100%
3	7	21	13	62%
4	2	8	4	50%
5	0	0	0	
6	1	6	6	100%
7	1	7	4	57%
Total	**24**	**56**	**33**	**33%**

Table 3

Risk factors for positive H7 serology of household members of influenza A/H7N7-infected persons, N = 56 (univariate analysis), The Netherlands, 2003

	Total no. of persons	No. of cases	RR	95 % CI	P value*
Female sex	34	17	0.7	0.5-1.04	0.091
Aged 19 years or over	36	21	0.97	0.6-1.5	0.90
Two or more toilets at home	45	31	3.8	1.1-13.5	0.0045
Pet bird inside home	7	7	1.9	1.4-2.5	0.034
Other pets living inside home	34	21	1.1	0.7-1.8	0.59
Use of cloth handkerchief	17	14	1.7	1.1-2.5	0.022
Use of paper handkerchief	27	12	0.61	0.4-0.99	0.034
Use of soap for handwashing	20	9	0.65	0.4-1.1	0.075
Good hygiene by index case	39	26	2.2	0.8-5.9	0.068
Poultry exposure by index case: 5 March + later	32	15	0.63	0.4-0.99	0.075
Sharing bedroom with others	40	22	0.8	0.5-1.3	0.43
Burning sensation in eyes	5	5	1.8	1.4-2.3	0.071
Smoking	5	5	1.8	1.4-2.3	0.071
Healthy, no medical history	36	18	0.67	0.4-1.0	0.068
Allergy in medical history	13	10	1.4	0.96-2.2	0.20
Use of oseltamivir	2	2	1.6	1.3-2.0	0.53
Conjunctivitis **	4	4	1.8	1.4-2.3	0.14
Influenza-like illness **	3	2	1.1	0.5-2.6	1.0

* P value using Fisher's exact test
** Association with, rather than risk factor for, positive H7 serology

infection confirmed by RT-PCR or serology, four of 62 household members (6.5%) met the possible case definition of conjunctivitis and all four cases (100%) had positive H7 serology.

The authors assume that the presence of H7-antibodies is indicative of a past AI A/H7N7 infection. This is supported by the results of another study in which the prophylactic use of oseltamivir was found to significantly reduce the seroprevalence of H7 antibodies in professionals exposed to infected poultry using the same serological test [12]. In that study, a significant association was found between the presence of H7 antibodies and the occurrence of eye symptoms, after correcting for prophylactic use of oseltamivir.

When using the adjusted HI assay, but not when using the microneutralisation assay, we detected a measurable antibody response in a high proportion of sera from persons exposed to laboratory-confirmed A/H7N7 infected persons. Evidence that these antibodies are real comes from three observations. First, any cross reaction of the A/H7 specific HI-assay with antibodies against A/H1 or A/H3 viruses would have been detected in the sera from persons recently vaccinated with the seasonal human influenza vaccine, but no reaction (0%) in the A/H7 HI assay was found. Second, as the sera of the recently vaccinated persons were collected in autumn 2002, just before the H7 epizootic started, the anti-H7 antibodies in the household contacts can not be explained as being the result of previous circulation of A/H7 virus. Third, none of the samples collected in autumn 2002 from 100 recently vaccinated persons had reactivity with the adjusted H7 assay [11]. This suggests that our results cannot be explained by aspecific reactivity of the adjusted HI-assay.

Our results suggest that during the outbreak of avian influenza A virus, subtype H7N7, household members of poultry workers were at increased risk of avian influenza either by direct (person to person) or by indirect (fomite) transmission. Previous observations of influenza transmission within households had shown secondary attack rates among household members of influenza cases in the same high range as observed in our study [13]. These high secondary attack rates are in contrast with findings for subtype A/H9N2 and A/H5N1, where no to limited secondary transmission was observed among healthcare workers and household contacts of cases [5,6,7,14,15]. However, we used a method for the detection of antibodies against the H7 virus which has a high analytical sensitivity. Detailed studies to analyse person to person transmission of H5 and H9 with the same methodology are sparse. Interestingly, for H9, a recent publication showed that in 44.6% of suspected cases of H9N2 infection and in 33.5% of the general population in Shantou city in China, antibody titres against H9 could be detected [16]. This observation suggests that secondary transmission of H9 viruses may be more common than has previously been assumed. In addition, the primary site of infection, the conjunctiva for H7 virus and the airway epithelium for H5 and H9 virus, and the possible difference in virus receptor expression on the conjunctiva and the airway epithelium together with the difference in affinity of the respective viruses for these receptors, may also account for the observed differences.

Although sharing bath towels and washcloths, and using cloth handkerchiefs seemed to increase the risk of clinical conjunctivitis, none of these observations was statistically significant, presumably due to lack of study power. However, it seems plausible to assume that patients with a viral conjunctivitis are more likely to expose household members to virus when sharing towels and washcloths or using cloth handkerchiefs. This is supported by our observation of higher seroprevalence among people using cloth handkerchiefs and of lower seroprevalence among those using paper (disposable) handkerchiefs, all of which were statistically significant. Studies on transmission of other viral conjunctivitis within households identified crowding and high numbers of persons per bathroom as risk factors [17, 18, 19, 20,21].

Seroprevalence was significantly higher among those who had at least two toilets in their homes than among those who had only one toilet. We have no explanation for this result. Hygienic measures, such as using soap for handwashing and good hygiene by the index case, associated with seropositivity were of borderline significance. Although we observed higher seroprevalence in those household members who had pet birds kept indoors at home, this cannot account for all seropositive secondary cases, as only 7 of all 33 cases had indoor birds at home. However, this finding raises the question of whether indoor pet birds could play a role in the household transmission of avian influenza virus, especially since six of seven cases with pet birds in the home were part of the same household. It is conceivable that these animals could serve as an amplifier for multiplication and shedding of the virus in the home environment. This deserves further attention in future outbreaks, for example, by monitoring and screening pet birds in the homes of poultry workers.

It was not possible to perform binomial regression for the outcome of A/H7N7 infection, presumably due to low numbers in the cohort.

If the detection of H7 antibodies is indicative for human (subclinical) influenza A/H7N7 infection, then the secondary spread of A/H7N7 to household contacts is on an unexpectedly large scale. Although the pathogenity of the A/H7N7 virus seemed to be low, the high transmissibility is directly related to an increased risk for double infection and reassortment. Current outbreak control measures did not take transmission to household contacts into account. This also raises the question of whether or not subclinical A/H7N7 cases can transmit the virus efficiently to other close contacts, which would imply that outbreak control strategy for A/H7N7 should be thoroughly revised. Consideration may be given to early isolation of cases and quarantine of contacts. Prophylactic treatment with oseltamivir should be considered for all household contacts of poultry workers during outbreaks of avian influenza, although its role must be further assessed in order to determine the risk of developing antiviral resistance. Moreover, in order to assess the role of fomites in secondary transmission of the A/H7N7 virus, further studies of contacts outside the household should be performed, as well as investigations to obtain background information on the spread of A/H7N7 in the general population of the Netherlands.

The study had the following limitations. Non-response was high and may be associated with rates of illness (selection bias), but we see no reason why it would have differed between exposed and non-exposed members of the cohort, therefore not biasing the estimate of the risk ratios. However, selection bias is not likely to play a major role with respect to seroprevalence, since most household members with detectable antibodies were asymptomatic.

In conclusion, our study suggests that human-to-human transmission of HPAI A/H7N7 can occur within household contacts in the absence of contact with infected poultry. Monitoring of clinical symptoms alone in household contacts of confirmed A/H7N7 cases underestimates the extent of human-to-human spread. In addition, our results suggest that cloth handkerchiefs, having indoor pet birds at home or having at least two toilets at home could be risk factors for household transmission A/H7N7 .

Taking all the results together, we recommend that during an outbreak of avian influenza: 1) Household members should be encouraged to use paper handkerchiefs instead of cloth handkerchiefs; 2) Household members of poultry workers exposed to A/H7N7 should be advised on enhanced general hygiene measures; 3) In the case that oseltamivir prophylaxis is offered to exposed poultry workers in future A/H7N7 epizootics, this should also be considered for household members of A/H7N7 cases; 4) Indoor pet birds of poultry workers should be screened and monitored during future outbreaks of avian influenza, in order to determine the role of indoor birds in household transmission of the virus; and 5) Further seroprevalence studies among contacts of asymptomatic persons with positive H7 serology should be conducted in order to assess the risk of person to person transmission, and consequently the potential for a new pandemic strain, in the absence of symptoms.

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ORIGINAL ARTICLES

Outbreak report

LATE DETECTION OF A SHIGELLOSIS OUTBREAK IN A SCHOOL IN MADRID

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Even though shigellosis in Spain is rare, an indigenous outbreak is occasionally detected. We describe an outbreak in a school in Madrid caused by person-to-person transmission of *Shigella sonnei*.
After the detection of *Shigella sonnei* in a stool sample from a 3 year old girl, an investigation at her school was initiated. Questionnaires were distributed to the parents of 520 pupils attending the school. A case was defined as a school case if it was the first case in a child's household, and as a household case if other members of the household had fallen ill first.

We identified 88 cases (60 pupils and 28 of their family members). The attack rate (AR) was 12% in the school and 32% in the families. There was a significant association between higher AR and lower age. The outbreak lasted for two months. The length and the shape of the epidemic curve of the 60 cases in pupils suggests person-to-person transmission. *Shigella sonnei* isolated from 5 different cases were typed by pulsed field gel electrophoresis (PFGE) and was found to be an identical strain. The prolonged duration of the outbreak was probably due to delayed detection, and stopped as soon as control measures were introduced.

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