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Risk factors for the introduction of high pathogenicity Avian Influenza virus into poultry farms during the epidemic in the Netherlands in 2003

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Abstract

An epidemic of high pathogenicity Avian Influenza (HPAI) occurred in the Netherlands in 2003. A census survey of 173 infected and 401 uninfected commercial poultry farms was carried out to identify factors associated with the introduction of the HPAI virus into poultry farms. Data on farm size, production characteristics, type of housing, presence of cattle and pigs were gathered by the National Inspection Service for Livestock and Meat from all farms included in this study. For each risk factor (RF) available for analysis, the Mantel–Haenszel odds ratio was calculated (stratified on farm size and housing type). We found an increased risk of HPAI virus introduction in layer finisher type poultry: OR = 2.05 (95% confidence interval, CI = 1.29–3.27). An explanation for this increased risk is the high number of contacts between these farms, especially via cardboard egg trays used for removal of eggs during the epidemic. Our analysis did not indicate significant differences between the infected and uninfected farms with regard to housing type, presence of cattle or pigs. Since layer

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finisher type farms are assumed to be at higher risk for HPAI virus introduction, more specific control measures might be applied in future outbreaks.

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1. Introduction

An epidemic of high pathogenicity Avian Influenza (HPAI) H7N7 started in the Netherlands on February 28, 2003 (OIE disease information, 2003). The regular control measures of the European Union (EU) (Council Directive 92/40/EEC, 1992) were implemented, such as depopulation of infected farms, a transport ban, and hygienic measures, in combination with pre-emptive culling of animals in farms within the regions (Stegeman et al., 2004). HPAI virus was isolated from 241 farms, but 1349 commercial farms and 16,490 backyard farms were depopulated, which resulted in the killing and destruction of 30 million birds. The poultry industry in the affected areas suffered substantial economic losses: the total costs amounted to 270 million euro (Dutch Ministry of Agriculture, Nature and Food Quality, 2003).

Controlling epidemics of notifiable diseases, in this case AI, by massive killing of mostly uninfected animals is criticised more and more, mainly on ethical grounds, and there is an increasing need for improvement of the current control measures. However, one reason for massive slaughter is a lack of knowledge about the mechanism of between-farm transmission of the infection. Therefore, the development of alternative control measures requires more insight in the routes of virus introduction into farms.

The current hypothesis about virus introduction is that low pathogenicity virus (LP AI), originating from wild migrating birds, is introduced into poultry and then mutates into a HPAI virus strain. This hypothesis has been described extensively (Hinshaw et al., 1979, 1980; Pomeroy, 1982; Alexander and Gough, 1986; Webster et al., 1992; Alexander, 1995; Alexander and Brown, 2000). HPAI virus may subsequently spread to other poultry farms via several routes, either via direct or indirect contact between poultry. In this respect, transport of live poultry, persons (Wells, 1963; Homme et al., 1970; Alexander and Spackman, 1979; Halvorson et al., 1980; Glass et al., 1981), and mechanical transfer of faeces of infected birds – in which very high virus concentrations are present (Utterback, 1984) – are considered to be the most important transmission routes. Consequently, these routes mainly consist of movements of people (e.g. farm owners and their staff), materials (e.g. egg trays) and vehicles (e.g. lorries that transport egg trays and eggs).

Other routes of transmission are via ‘contiguous spread’, a comprehensive term that includes transmission from infected farms over short distances by unknown or poorly understood introduction routes (Henzler et al., 2003). Finally, interspecies transmission via pigs is also considered to be a source of infection to poultry (Scholtissek et al., 1983; Webster et al., 1992; Wright et al., 1992; Brown et al., 1993, 1997; Kida et al., 1994; Guan et al., 1996, 2002; Karasin et al., 2000; Olsen et al., 2000; Webby et al., 2000; Peiris et al., 2001; Ninomiya et al., 2002).

However, although many routes of virus introduction were identified, the relative importance of each route, which is essential for the improvement of existing control

measures, remains unknown. The 2003 HPAI epidemic in the Netherlands offered an opportunity to explore and quantify risk factors (RF) for introduction of HPAI into poultry farms. During this epidemic, data were gathered for tracing purposes, which might allow further analysis. Moreover, technical data on all 'uninfected' farms were available. The goal of this study was to identify and quantify risk factors for introduction of HPAI into poultry farms from the available census survey data.

2. Materials and methods

2.1. Study population

Outbreaks occurred in three different regions of the country. In this study, we used data on poultry farms located in the central part of the Netherlands (Gelderse Vallei/Beneden Leeuwen). One reason to use only this region was that most outbreaks by far occurred there (198 virus-positive flocks in contrast to 34 in Limburg province and 2 isolated ones). A second reason was that this area was the only one to be depopulated as a whole, and, consequently, data about all farms were gathered. A final reason was that farm management practices in this area with relatively small mixed farms were more comparable. Management in the Limburg area with relatively large poultry-only farms was expected to be different.

We included only commercial chicken farms in this analysis and excluded backyard poultry. Our dataset lacked reliable information on non-commercial backyard flocks.

Farms without clinical signs and without antibodies to H7 AI virus at depopulation by HA/HI were defined as controls. Farms with clinical signs and a positive high pathogenicity H7N7 AI virus isolation status by RT-PCR were defined as infected ([OIE manual of diagnostic tests and vaccines for terrestrial animals, 2004](#)). A total of 574 commercial chicken farms were available for the study: 173 cases and 401 controls.

2.2. Study design

We used data that were collected routinely by the National Inspection Service for Livestock and Meat (RVV), the Dutch government agency responsible for the control of notifiable diseases. The data were gathered by use of standardised forms during various visits related to screening, tracing or depopulation, to infected and uninfected farms. These visits are obliged according to EU regulations, and are not carried out for research purposes. Approximately 25 trained government veterinary officials carried out the visits related to tracing. Seventy-five untrained officials performed the visits to unsuspected farms for non-tracing purposes, using the same forms. The forms that were used for all previously mentioned aims were not pretested in any scientific way. Full questionnaires, in Dutch, are available from the first author.

Our data set contained information on AI status, farm size (number of animals and number of poultry houses), production characteristics of meat type and layer type poultry (breeders, growers, finishing birds), type of housing (battery cages, ground floor system, free-range system), and presence of cattle and pigs.

Backward tracing of possible sources was also carried out by the RVV. Despite all effort, however, most of the infection routes remained unclear or could not be allocated to one source only. We wanted to study introduction routes that had not been gathered in the data set and we wanted to study them individually. For that purpose, we had to use plausible quantitative derivatives (hereafter called risk factors) of possible routes of virus introduction, as mentioned previously.

2.2.1. Risk factor definition

We hypothesised that introduction of HPAI into a flock could be caused by, in order of relative importance:

- 1) Poultry transports.
- 2) Neighbourhood infection. This route of virus spread is generally used, but the exact mechanism is unknown. This route is defined as transmission over a short distance via various, but unknown routes.
- 3) Personnel who, as a profession, deal with poultry in particular and as such are prone to enter the houses (e.g. farm helpers, information officials and egg transporters) hereafter called poultry professionals.
- 4) (a) Infected wild birds, or (b) mechanical transfer of faeces of infected commercial poultry by wild birds or vermin. We presumed that wild birds or vermin could transfer the virus to commercial poultry via free-range systems, or into the courtyard. Consequently, farmers could transfer the virus via their boots into ground floor systems or free-range housing systems.
- 5) Pigs on mixed farms with poultry. On these farms, pigs could have infected the poultry.

As poultry transport was prohibited from the time of the first report (February 28) onward, we did not explore the first route. The second route was not open to investigation either, because geographical information system (GIS) data on farm locations were not available. Thus, three possible introduction routes of AI virus remained to be studied (3–5).

The five risk factors chosen as derivatives of the remaining hypothesised introduction routes were:

- Ad 3) Farms with layer type chickens (producers of table eggs), because, during the epidemic, poultry professionals associated with egg transport visited these farms more often than other types of farms (RF 1 & 2).
- Ad 4) a) Free range farms, and b) mixed farms with cattle without free-range housing for the poultry. Mixed cattle farms were chosen, because we expected an increased number of farmers' activity around the courtyard as compared to commercial poultry-only-farms. We also expected roughage to be present on farms with cattle, thus attracting wild birds and vermin (RF 3 & 4).
- Ad 5) Mixed farms with pigs (RF 5).

These risk factors were corrected for confounding by farm size and housing type.

Table 1

Confounding factors and strata regarding risk factors for introduction of AI virus into poultry farms in the study population during the 2003 HPAI epidemic in the Netherlands

Risk factor	Confounder	Strata	Strata, specified
Layer finisher chickens	Housing type	[Battery; ground floor system]	–
	Farm size	[Small; large]	1 house; >1 house
All layer type chickens	Housing type	[Battery; ground floor system]	–
	Farm size	[Small; large]	1 house; >1 house
Free-range housing	Housing type	[Battery; ground floor system]	–
	Farm size	[Small; large]	≤9315 birds; >9315 birds
Mixed farms with cattle	Housing type	[Battery; ground floor system]	–
	Farm size	[Small; large]	1 house; >1 house
Mixed farm with pigs	Housing type	[Battery; ground floor system]	–
	Farms size	[Small; large]	1 house; >1 house

2.3. Data analysis

The five risk factors were first evaluated by calculating the crude odds ratio (OR) and 95% confidence intervals (CI). Secondly, the OR was adjusted for confounding by other suspected variables, using the Mantel–Haenszel procedure to produce an adjusted OR (Mantel and Haenszel, 1959). For adjusted OR, farms were grouped into strata of expected confounders (Table 1). The stratum-specific estimates were considered similar enough for pooling if the Breslow–Day statistic was not significant ($p > 0.05$) (Breslow and Day, 1980). An association was considered statistically significant if the probability that it arose from chance was <0.05 . Data were analysed with SPSS10 (SPSS for Windows, Standard Version, 1999).

3. Results

After data control, the final study population consisted of 574 depopulated commercial farms: 173 cases and 401 uninfected control farms. The majority (85%) were layer type poultry, the remaining farms (15%) meat type poultry. Approximately half of the farms also kept other intensively farmed livestock: 47% of these were mixed cattle farms, 30% mixed pig farms and 23% had more than one type of livestock other than poultry (Table 2).

The median farm size expressed as the number of poultry houses was one (minimum 1–maximum 9), and 9315 (4–193257) expressed as the number of birds (Table 3). Twenty-seven percent of the farms housed their birds in battery systems, and 72% in ground floor systems (the remaining 1% of the data on housing type was missing). Eighteen percent of the farms with a ground floor system also had a free-range system (Table 2).

Of the five risk factors under study, the presence or absence of layer finisher type chickens was found to be significantly associated with the risk of HPAI virus introduction (OR = 1.65, 95% CI = 1.06–2.56). Stratified analysis on the basis of type of housing did not alter the direction or size of the association. Stratification on farm size did alter the size of the association, albeit not significantly (Table 4). Results from multivariable logistic regression (not shown) were very similar to those of the Mantel–Haenszel procedure.

Table 2

Poultry farm characteristics of cases and controls from data collected in the study population during the 2003 HPAI epidemic in the Netherlands

Characteristic	Number of	
	Cases	Controls
Total	173	401
Hobby poultry next to commercial poultry		
Yes	9	31
No	164	370
Type of commercial chickens		
Meat type chickens only	24	64
Layer type chickens only	149	337
Of which layer finisher chickens only	141	292
Type of housing		
Battery cages only	49	106
Ground floor system only	119	292
Of which free-range only	24	49
Missing	5	3
Other livestock		
Pigs only	25	58
Cattle only	47	84
>1 type of other livestock	14	51
No other livestock	81	202
Missing	6	6

4. Discussion

The aim of this paper was to quantify the association between predefined risk factors and the introduction of HPAI virus into poultry farms during the epidemic in the Netherlands in 2003. We did not want to carry out a ‘fishing expedition’ on all the potential risk factors as recorded by the RVV, due to the expected bias in the dataset.

Table 3

Farm size expressed as number of birds as well as number of poultry houses on poultry farms from data collected in the study population during the 2003 HPAI epidemic in the Netherlands

Farm size	Farm size, applied to	Minimum	25th centile	Median	75th centile	Maximum	Mean
Number of birds	Total study population	4	4255	9315	21825	193257	17571
	Cases	47	6384	12962	28253	158684	20868
	Controls	4	3450	8025	17431	193257	16157
Number of houses	Total study population	1	1	1	2	9	1.8
	Cases	1	1	2	3	6	2.0
	Controls	1	1	1	2	9	1.6

Table 4
Activities and exposures associated with HPAI infection of poultry farms from data collected in the study population during the 2003 HPAI epidemic in the Netherlands

Risk factor	# Cases with risk factor (total # cases available)	# Controls with risk factor (total # controls available)	OR ^a	95% CI ^b	OR _{MH} ^c	95% CI
Layer finisher chickens (1) vs. all other chicken types (0)	141 (173)	292 (401)	1.65	1.06–2.56	2.05 ^d , 1.69 ^e	1.29–3.27, 1.06–2.68
All layer type chickens (1) vs. all meat type chickens (0)	149 (172)	337 (401)	1.23	0.74–2.06	1.59 ^d , 1.30 ^e	0.93–2.71, 0.76–2.23
Free-range housing (1) vs. all other housing types (0)	24 (170)	49 (398)	1.17	0.69–1.98	1.34 ^d	0.78–2.29
Cattle (1) vs. No cattle (0) on farms without free-range housing for chickens	52 (143)	116 (346)	1.13	0.75–1.70	1.28 ^d , 1.14 ^e	0.84–1.95, 0.76–1.72
Mixed farms with pigs (1) vs. farms without pigs (0) regardless the absence or presence of other farm animals	40 (168)	110 (396)	0.81	0.54–1.23	0.90 ^d , 0.79 ^e	0.59–1.39, 0.51–1.20

^a OR, odds ratio.

^b 95% CI, 95% confidence interval.

^c OR_{MH}, OR Mantel-Haenszel.

^d Stratified on farm size.

^e Stratified on housing type.

A significant association between layer-finisher type poultry and the presence of HPAI virus was found in this analysis, where this risk factor was defined to approximate a large number of human contacts. The causal factor behind this association might be inadequate hygiene measures taken by lorry drivers between farm visits, for example by reuse of egg crates, which was also suggested by Alexander (1995), albeit qualitatively. More precise information on farms with layer-finisher type poultry was unavailable, because all the farms were depopulated, and farmers were not revisited. It was not possible to quantify the association between either poultry transports or area spread and introduction of AI virus, because these data were not available.

Some factors expected to be important for the introduction of AI virus did not show up in our analysis. In contrast to the qualitative suggestions made by Lang (1981) and Pomeroy (1982), we did not find an increased risk of HPAI virus introduction in free-range systems. However, this lack of finding may well have been caused by the obligation to keep all poultry inside after the first outbreak was diagnosed. We intended to study the period before and after detection of the first outbreak separately, but we lacked data on timing of the HPAI virus introduction per flock and therefore also would not have been able to select proper controls.

Mixed farms with cattle or pigs were not significantly associated with a higher risk of HPAI virus introduction. Possibly, the hypothesis of transmission via vermin or contiguous contact was not appropriate, or the hygienic measures on these farms were more stringent. Another possibility is that a certain number of the contacts were not poultry-related.

This study contained possible restrictions regarding the inclusion criteria for the study population, confounding and misclassification. Although many backyard or hobby farms were depopulated, we included only depopulated commercial farms in our study population. Most likely, because of the contact structure and the small size of the 'flocks', their role in the epidemic is probably negligible and commercial farms were expected to be better comparable to each other regarding risk management related to infectious diseases. Moreover, no data were gathered from most of the depopulated backyard farms.

We identified farm size and housing type as possible confounders in this study. Although literature on Avian Influenza does not report accordingly, from observational studies on transmission of infectious diseases in intensively reared stock, a tendency arises for larger farms to become infected more often with infectious disease agents than small farms (Refregier-Petton et al., 2001; Kaneene et al., 2002; Akey, 2003; Dewey et al., 2003) and thus farm size being a risk factor for the presence of these agents. In our study, we did explore farm size as a risk factor for introduction of HPAI virus. The number of houses was significantly associated with the presence of HPAI virus (OR = 1.93, 95% CI = 1.34–2.79), and also the number of animals (OR = 2.08, 95% CI = 1.45–3.00). The mechanism behind this risk factor is that although the probability of infection of an individual bird as such is generally very small, on large farms with many animals and many animal contacts, the chance of actual infection of the herd is greater than on small farms with a limited number of animals. We therefore expected farm size to be a risk factor, and a source of confounding, which it was as it altered associations.

Housing type could be of specific interest, because 75% of layer type poultry in the Netherlands are in ground floor systems of which 58% are in free-range systems (Statistics Netherlands, 2002). In this study, housing type was a risk factor, and no source of

confounding. Possibly, farmers with ground floor systems realised they were more at risk for introduction of AI virus and took appropriate hygiene measures to prevent it or the number or type of contacts did not differ between battery or ground floor systems. Moreover, poultry was housed inside immediately after the first outbreak was detected, reducing the probability of this introduction route.

It should be noted that, as regards our case-control definition, some controls theoretically could have been infected with HPAI virus without showing clinical signs, leading to differential misclassification and thus either underestimation or overestimation of association between risk factors and infection of AI. As both transmission rate as well as mortality rate of the H7N7 HPAI virus were very high, it seems unlikely that clinically healthy flocks were infected. Furthermore, compared to the infected farms, accuracy in data collection was probably less in undetected or unsuspected farms because of the tendency to be more precise on infected farms for backward tracing purposes. This could lead to differential misclassification and thus either underestimation or overestimation of association between risk factors and infection of AI. Our dataset, however, contained mainly data of a technical nature so we expect this phenomenon – if present – to be limited.

For future outbreaks of HPAI, our findings suggest that the contacts between layer type farms should be limited as much as possible, and might be a first step in a more sophisticated approach to eradication of the AI virus from the poultry population. In practice, if the current depopulation policy is upheld, either prioritisation of high-risk farms and their contacts at depopulation in a certain radius around infected farms or prohibition of the collection of eggs might decrease mechanical transmission.

We have shown that routinely collected data for other than research purposes, could be of use in quantification of introduction routes of HPAI virus. More research on this topic is recommended, either prospective or otherwise, to be able to further quantify all routes.

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