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Review

The risk factors for avian influenza on poultry farms: A meta-analysis

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ABSTRACT

Background: Avian influenza is a severe threat both to humans and poultry, but so far, no systematic review on the identification and evaluation of the risk factors of avian influenza infection has been published. The objective of this meta-analysis is to provide evidence for decision-making and further research on AI prevention through identifying the risk factors associated with AI infection on poultry farms.
Methods: The results from 15 selected studies on risk factors for AI infections on poultry farms were analyzed quantitatively by meta-analysis.
Results: Open water source (OR = 2.89), infections on nearby farms (OR = 4.54), other livestock (OR = 1.90) and disinfection of farm (OR = 0.54) have significant association with AI infection on poultry farms. The subgroup analysis results indicate that there exist different risk factors for AI infections in different types of farms.
Conclusions: The main risk factors for AI infection in poultry farms are environmental conditions (open water source, infections on nearby farms), keeping other livestock on the same farm and no disinfection of the farm.

1. Introduction

Avian influenza is a severe infectious disease caused by the AI virus. Both humans and animals can be infected (Gao et al., 2013), and the mortality rate is high in both humans and poultry. Since the first human infected case, detected in 1997 during a poultry outbreak in Hong Kong SAR, China, there have been to date 380 deaths worldwide out of 641 cases caused by the H5N1 virus subtype (WHO, 2013). Thus, avian influenza could cause enormous health and economic losses worldwide, and it has been classified as a List A disease by the Office International Des Epizooties (OIE). AI has been known for more than 100 years, but its control measures remain limited. Disinfection, isolation and culling are the only measures available to prevent its spread. The WHO's monitoring data and many other relevant studies show that AIV can transmit from birds to people but not vice versa (Perdue and Swayne, 2005). Therefore, controlling AI in poultry is the first step in decreasing risks to humans. Some scholars have conducted epidemiological studies on risk factors for AI in poultry, but some of the results are inconsistent and even contradictory. Moreover, thus far, no one has conducted a systematic review of the association between AI and

Abbreviations: OR, odds ratio; AI, avian influenza; AIV, avian influenza virus; CI, confidence interval.

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production, management, environment and biological factors on poultry farms. By the retrieval, screening and comprehensive analysis of the published epidemiology studies on the identification of AI risk factors on poultry farms, this study attempts to adopt a systematic approach to identifying the risk factors for AI infection and to provide a basis for decision-making and for further research on AI prevention.

2. Materials and methods

2.1. Search strategy

Systematic research was performed on the literature about risk factors for AI on poultry farms. The databases included PubMed, Wiley, Elsevier, Springer and Cochrane Library. Based on the reported AIV subtypes in poultry (Alexander, 2007, 2000; Perdue and Swayne, 2005; Swayne, 2008), the basic logic relationship of keywords in the database retrieval was (risk) AND (avian influenza OR HPAI OR LPAI OR H5N1 OR H5N2 OR H5N3 OR H5N8 OR H7N1 OR H7N3 OR H7N4 OR H7N7 OR H7N9 OR H9N2), etc. Based on the earliest traceable report of AI (Swayne and Suarez, 2000), the retrieval dates were limited to the period from January 1955 to May 2013, and the retrieval language was limited to English. Finally, the authors searched the original articles, review articles and references cited from the retrieved articles.

2.2. Study selection

Under the premise of equilibrium between the studies' internal validity and extrapolation, based on Lichtenstein's 20 standards (Lichtenstein et al., 1987) and experts' discussion, the following literature inclusion and exclusion criteria were set.

Inclusion criteria: (1) The 1: N matched case-control studies were on AI risk factors in China and overseas. (2) The publishing date ranged from 1955 to 2013. (3) The respondent of study was on the farm level, not on the poultry level. (4) The definitions of exposures were clear and the same. (5) The sample size was specified. (6) The outcome was AI infection. (7) The associative indicator between exposure and outcome was OR, and either the original data provided OR values with 95% CIs or other data could be converted to ORs and their 95% CIs.

Exclusion criteria: (1) The sample size of the study's case or control group was less than 10. (2) The study had incomplete or inconsistent data. (3) Publications with results that have been published before.

Following the above criteria, the initial selection was made by two authors (Y.M.W. and P.L.) independently, and any disagreements were resolved by consensus.

2.3. Data extraction

The following data were extracted from the selected studies: the first author, publication year, country, sample source, case-control study time, type of farm, type of poultry, subtype of AIV and its pathogenicity, exposure factors, and number of exposed and nonexposed cases in the case-control study. To avoid misclassification caused by unclear definitions of exposure in various studies, some exposure factors were defined as follows: (1) confinement: farms were surrounded by fencing. (2) Visitors enter the farm: family and friends entered the farm without disinfection or cloths changing. (3) Shared equipment: the equipment, such as transportation and coops were also used by other farms. (4) Open water source: untreated ponds and rivers existed in the surrounding areas to which the poultry could have direct or indirect contact. (5) Near farm infection: there were cases of infection with avian influenza near the farm. (6) Backyard poultry: there were cage-free poultry on farm. (7) Bird contact: there were bird droppings or bird-damaged feed around farms without bird-proof facilities. (8) Other livestock on farm: there were other livestock, such as cattle or sheep on farm. (9) Hygiene manners of farm workers: farmers changed their clothes and shoes and washed hands when they went to work. (10) Disinfection of transportation: vehicles went in and out of the farm were disinfected (tires should be disinfected, too). (11) Disinfection of farm: disinfectants were regularly used to clean the yard, coops and so on. (12) Appropriate disposal of dead poultry: the safety measures used to dispose of ill and dead poultry, such as deep burial, incineration and composting.

In the process of data extraction, ambiguous and missing data were clarified and obtained by contacting the corresponding authors, and then, all data were extracted by double entry and validation.

2.4. Statistical analysis

The software Review Manager 5.2 was used to conduct meta-analysis of the extracted data. The merged effect was OR and its 95% CI, which reflected the strength of association between exposures and AI. The χ^2 test was used for the homogeneity test. In consideration of the facts that the quantity of selected studies was limited and the Q statistic's power was low, the significance level (α) was set to 0.10 to increase the power and reduce the probability of false negatives. Because the number of studies in this analysis was small, which limits the accuracy of the homogeneity test, we could not tell whether the studies were functionally equivalent (Borenstein et al., 2009; Xu, 1994); therefore, we used the random effect model to estimate the overall OR of all studies. At the same time, subgroup analysis was used to compare the change in heterogeneity before and after the selected studies being stratified by different farm types. Next, to analyze the sensitivity of the results, we used the one-removed study method to show the impact of each study on the overall OR. To detect publication bias, the fail-safe N method was used to calculate the number of studies that would have been needed to reverse the effect (Mai et al., 2006), and the Egger's regression test was used to investigate the association between sample size and effect size (OR value) and quantitatively detect the publication bias (Egger et al., 1997).

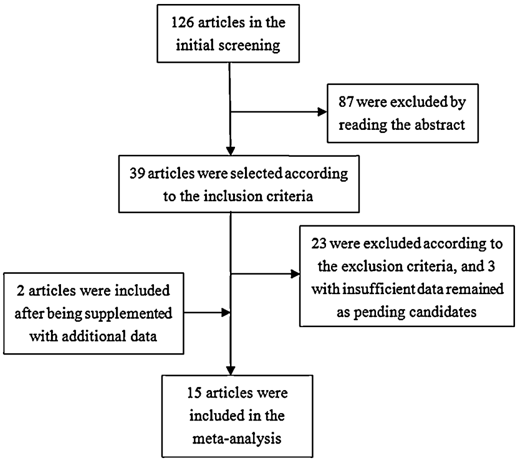

Fig. 1. Study selection process.

3. Results

3.1. Description of studies included

A total of 126 studies were found, from which 87 were excluded at the initial screening. Among the 39 remaining selected articles, three of them studied beyond poultry farms, two papers gave ambiguous definitions of exposure, another two studies were repeated, and nineteen articles did not provide sufficient data. Subsequently, two studies were supplemented by contacting the corresponding authors. Finally, 15 studies were selected, and these studies surveyed 2823 farms from 11 countries and regions on 4 continents, with 843 being case farms (Fig. 1 and Table 1).

3.2. Results of meta-analysis

3.2.1. The overall OR values

The factors of open water source, nearby farm infection, other livestock on farm and disinfection of farm showed significant associations with AI infection ($P < 0.05$) (Table 2). Open water source, nearby farm infection, and other livestock on farm were risk factors (OR > 1), and disinfection of farm was a protective factor (OR < 1) for AI infection on poultry farms.

3.2.2. Subgroup analysis

There were significant heterogeneities among the studies that included the factors of visitors enter the farm, shared equipment, birds, other livestock on farm and disinfection of transportation ($P < 0.1$) (Table 2). For the heterogeneous studies that included these factors, the meta-analysis was stratified by different farm types. In contrast with the results prior to stratification (Table 3), the association between the factor of other livestock and AI infection on commercial and small-scale farms had no statistical significance ($P = 0.52$ and 0.10, respectively).

3.3. Sensitivity analysis

With the factors that had significant associations with AI infection, overall OR values' stability and reliability were evaluated by removing one study at a time to compare the changes in the overall OR values. For the factors of open water source and nearby farm infection, the changes to their overall OR were small, while for the other two factors, the estimates were sensitive and not stable (Table 4).

3.4. Publication bias

The fail-safe N method and the Egger's regression test were used to detect publication bias in the studies that included the factors whose overall OR values had statistical significance (Table 5). If there had been publication bias, to reverse the effects of open water source, nearby farm infection, other livestock on farm and disinfection of farm, at least 65, 119, 45 and 32 studies, respectively (particularly studies with negative results) would have been necessary ($P = 0.05$). In the Egger's regression test, the size of the intercept represents the degree of the funnel plot's asymmetry, and the P value ($P > 0.05$) reflects there was no significant association between sample size and effect size, which means no obvious publication bias exists in this meta-analysis.

4. Discussion

AI epidemics in poultry can seriously impact local and global economies and international trade. Occurrences of bird-to-human transmission of AIV have increasingly been reported in recent years, culminating in the outbreak of influenza A (H5N1 and H7N9) among poultry in several Southeast Asian countries with associated human infections. What is more, the mortality rate is very high in both humans and poultry, and thus, it is necessary to further study the epidemiology of AI in poultry. Therefore, we used the meta-analysis method to explore the risk factors for AI infection on poultry farms. We hope that our study can provide AI and other poultry disease researchers with some reference and assistance.

4.1. Evaluation of study quality

Meta-analysis can quantitatively merge and synthetically evaluate the results of multiple independent studies, which can make up for any deficiency in a single study's relative dispersion of effect value and confidence interval (Petitti, 1994) and thereby obtain a reliable and comprehensive conclusion. Based on Lichtenstein's 20 standards, expert discussions and the above inclusion and exclusion criteria, we discussed the reasonability of each study's design, the representation and size of each sample, the definitions of exposure, and the correctness of statistical methods, as well as controls for bias and confounding factors, and so on, which effectively guaranteed the reliability of the results of this meta-analysis.

Table 1
Profile of the 15 selected studies.

Number	Author (year), country	Retrospective time	Farm type	Species	AIV subtype	Pathogenicity	Case number/control number
1	McQuiston et al. (2005), USA	2002	Commercial	Chicken, turkey	H7N2	Low	151/199
2	Woo and Park (2008), Korea	2005–2006	Commercial	Chicken, duck	H9N2	Low	25/71
3	Fasina et al. (2011), Nigeria	2006–2007	Commercial	Layer chicken	H5N1	High	32/83
4	Henning et al. (2009), Vietnam	2007	Small-scale	Chicken, duck	H5N1	High	22/44
5	Paul et al. (2011), Thailand	2004–2005	Backyard	Chicken	H5N1	High	104/382
6	Thomas et al. (2005), Netherlands	2003	Commercial	Chicken	H7N7	High	173/401
7	Thompson et al. (2008), South Africa	2005	Commercial	Ostrich	H5N2	High	82/285
8	Biswas et al. (2009a), Bangladesh[a]	2007	Backyard	Chicken	H5N1	High	25/75
9	Kung et al. (2007), Hong Kong	2002	Commercial	Chicken	H5N1	High	16/46
10	Desvaux et al. (2011), Vietnam	2007	Backyard	Chicken	H5N1	High	19/19
11	Nishiguchi et al. (2007), Japan	2005	Commercial	Layer chicken	H5N2	High	37/36
12	Osmani et al. (2013), Bangladesh[a]	2011	Commercial	Layer chicken	H5N1	High	90/175
13	Lohiniva et al. (2012), Egypt	2009	Small-scale	Chicken, duck and pigeon	H5N1	High	19/18
14	Biswas et al. (2011), Bangladesh[a]	2008	Small-scale	Chicken	H5N1	High	15/45
15	Biswas et al. (2009b), Bangladesh[a]	2007	Commercial	Chicken	H5N1	High	33/99

[a] Although these four studies were conducted in the same country, the poultry species, farms, retrospective times and specific survey areas were not the same.

Table 2
Results of the homogeneity test of the selected studies and strength of association (overall OR) between exposure and AI infection on poultry farms.

Exposures	Homogeneity test	OR (95% CI)	Selected studies
Farm's administration			
Confinement	$P = 0.56$, $I^2 = 0\%$[a]	0.80 (0.60, 1.06)	1,3,11,12,14
Visitors enter the farm	$P < 0.01$, $I^2 = 76\%$	1.47 (0.40, 5.35)	3,4,9,11,14,15
Shared equipment	$P = 0.02$, $I^2 = 64\%$	1.63 (0.95, 2.79)	1,3,5,7,11,12
Farm's environmental condition			
Open water source	$P = 0.54$, $I^2 = 0\%$[a]	2.89 (1.98, 4.21)[b]	3,4,5,7,8,10,13
Nearby farm infection	$P = 0.68$, $I^2 = 0\%$[a]	4.54 (2.73, 7.56)[b]	3,4,9,11,14
Contact with other animal			
Backyard poultry	$P = 0.67$, $I^2 = 0\%$[a]	1.05 (0.83, 1.34)	1,5,6,7,12,14,15
Birds	$P < 0.01$, $I^2 = 62\%$	1.14 (0.66, 2.00)	1,2,3,4,7,8,9,11,14,15
Other livestock on farm	$P = 0.01$, $I^2 = 62\%$	1.90 (1.07, 3.37)[b]	3,4,5,6,10,11,13
Biosecurity			
Hygiene manners of farm workers	$P = 0.15$, $I^2 = 35\%$[a]	0.91 (0.57, 1.45)	1,2,3,11,12,13,14,15
Disinfection of transportation	$P = 0.07$, $I^2 = 54\%$	0.95 (0.57, 1.61)	1,3,7,11,15
Disinfection of farm	$P = 0.45$, $I^2 = 0\%$[a]	0.54 (0.37, 0.78)[b]	2,3,4,5,8,11,15
Appropriate disposal of dead poultry	$P = 0.16$, $I^2 = 41\%$[a]	0.81 (0.45, 1.46)	3,8,12,15

[a] No significant heterogeneity among selected studies ($P > 0.1$, $I^2 < 50\%$).
[b] The overall OR values have statistical significance ($P < 0.05$).

4.2. Discussion of meta-analysis

This study demonstrates that the main risk factors for AI infection on poultry farms are environmental conditions (open water sources, infections on nearby farms), keeping other livestock on the same farm and not disinfecting the farm. First, the surrounding environment's significant impact on AI infection on poultry farms shows that scientific locations and the rational distribution of farms are important for preventing AI. Second, the relevant studies showed that pigs, horses, leopards, mink and other livestock and wildlife are also the natural reservoir of AIV

Table 3
Results of subgroup analysis calculated by different farm types.

Factors	Type of farms	Homogeneity test	Overall OR (95% CI)	Selected studies
Visitors enter the farm	Commercial	$P = 0.01$, $I^2 = 76\%$	2.87 (0.68, 12.10)	3,9,11,15
	Small-scale	–	0.21 (0.04, 1.21)	4,14
Birds	Commercial	$P = 0.28$, $I^2 = 20\%$[a]	1.09 (0.74, 1.62)	1,2,3,7,9,11,15
	Small-scale	$P = 0.02$, $I^2 = 82\%$	0.45 (0.02, 9.10)	4,14
Other livestock on farm	Commercial	$P = 0.02$, $I^2 = 74\%$	1.35 (0.54, 3.38)	3,6,11
	Small-scale	$P = 0.86$, $I^2 = 0\%$[a]	2.76 (0.83, 9.21)	4,13
	Backyard	$P = 0.26$, $I^2 = 22\%$[a]	2.71 (1.29, 5.71)[b]	5,10

[a] No significant heterogeneity among selected studies ($P > 0.1$, $I^2 < 50\%$).
[b] The subgroups' overall OR values have statistical significance ($P < 0.05$).

Table 4
The changes to the overall OR by removing one study at a time.

Removed study	Overall OR (95% CI)			
	Open water source	Nearby farm infection	Other livestock on farm	Disinfection of farm
–	2.89 (1.98, 4.21)	4.54 (2.73, 7.56)	1.90 (1.07, 3.37)	0.54 (0.37, 0.78)
2	–	–	–	0.48 (0.32, 0.72)
3	2.85 (1.91, 4.27)	5.14 (2.76, 9.58)	1.62 (0.93, 2.83)	0.52 (0.34, 0.81)
4	2.90 (1.96, 4.30)	4.77 (2.70, 8.42)	1.83 (0.99, 3.39)	0.59 (0.39, 0.87)
5	2.54 (1.56, 4.15)	–	1.91 (0.93, 3.92)	0.56 (0.31, 1.01)
6	–	–	2.30 (1.14, 4.62)	–
7	3.16 (2.12, 4.72)	–	–	–
8	2.72 (1.81, 4.09)	–	–	0.51 (0.33, 0.79)
9	–	4.68 (2.71, 8.08)	–	–
10	2.87 (1.95, 4.23)	–	1.67 (0.95, 2.95)	–
11	–	4.25 (2.36, 7.65)	2.33 (1.28, 4.25)	0.56 (0.36, 0.87)
13	3.08 (2.10, 4.52)	–	1.89 (1.02, 3.50)	–
14	–	4.09 (2.40, 6.96)	–	–
15	–	–	–	0.56 (0.36, 0.87)

Table 5
Results of publication bias detection.

Factors	Number of studies	Fail-safe number[a]	Egger's regression test	
			Intercept	P
Open water source	7	65	−1.50	0.130
Nearby farm infection	5	119	1.99	0.218
Other livestock on farm	7	45	1.66	0.163
Disinfection of farm	7	32	−1.14	0.377

[a] The number of studies required to reverse the effects are calculated on the condition of $P = 0.05$.

(Olsen et al., 2006; Zhou and He, 2009), and these findings are similar to our result that keeping other livestock on the same farm may increase the risk of AI infection. Therefore, perimeter fencing and proper production practices are suggested. Third, regular disinfection of farm had lower odds of infection, compared with no disinfection of farm (OR = 0.54; 95% CI = 0.37, 0.78). One explanation we can offer for this association is that some kinds of disinfectants (e.g., the compounds of chlorine, aldehydes and quaternary ammonium) can be against the influenza virus effectively (Tiensin et al., 2005). Lastly, although farm administration factors such as confinement, shared equipment and biosecurity (except disinfection of farm) did not show any significant associations with AI infection, their P-values were small, given the small number of included studies; Therefore, we should establish and strengthen standard management rules in the process of epidemiological surveillance and prevention.

Furthermore, to obtain more reasonable results, we tentatively regarded farm type as a heterogeneous influence factor so that we could conduct the subgroup analysis to compare the change in heterogeneity before and after the selected studies being stratified by different farm types. The results showed different OR values on the different types of farms. This further confirms that subgroup analysis can reduce the heterogeneity of selected studies, and it also suggests that different management practices should be adopted according to different types of farms.

The method of removing one study at a time (Table 4) indicates that the estimates were stable for risk factors open water source and nearby farm infection. Nevertheless, the significance level of the other two variables changed when some of the studies were removed. This indicates a lack of stability of these estimates and warrants further investigation of the impact of these risk factors.

Through funnel plotting the studies, potential publication bias could be detected visually, but the funnel plot was insufficient to assess the bias, especially when only a small number of studies were included (Thornton and Lee, 2000); meanwhile, using the fail-safe N method, the number of studies needed to reverse the effect can be calculated quantitatively, but this method cannot calculate the number of studies that are needed to nullify the effect, and it has low power (Li and Wang, 2008; Rothstein, 2008). Therefore, we also used the Egger's regression test to quantitatively assess the symmetry of the funnel plot, and the result indicated that there was not publication bias in the studies.

4.3. Limitations

In general, under the condition of more than 10 included studies, meta-regression is recommended to identify and process the factors that cause heterogeneity (Higgins et al., 2002; Schmid et al., 2004). Unfortunately, we could not obtain a sufficient number of studies. Therefore, for the subgroup analysis, we tentatively selected confounding factors based on experience and authors' discussion. Of course, in addition to farm type, there may have been other confounding factors in our study (e.g., survey area or pathogenicity of AIV). However, because the surveyed areas of the included studies focused on Southeast Asia and nearly 90% of the outcomes were HPAI, it was difficult to control the impact of the different areas and different pathogenicities on the results. Therefore, more informative data are needed to identify confounding factors and to confirm whether there are different risk factors in different areas and different pathogenicities of AIV.

In addition, given that there are so few epidemiological studies of the risk factors for AI among poultry farms and that the quality requirement of studies for meta-analysis is high, only 15 articles were included in this analysis, with most of the survey areas in Southeast Asia. Therefore, any practical guiding significance is limited for other areas (especially Europe and South Africa).

Based on the above limitations, we are conducting epidemiological investigations and studies on AI risk factors in China. At the same time, to further supplement and improve the analysis and evaluation, we are also looking forward to receiving additional updates on relevant studies.

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