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Original Article

Highly pathogenic avian influenza A(H5N1) in animals: A systematic review and meta-analysis

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ABSTRACT

Introduction: Avian influenza A H5N1 is a significant global public health threat. Although relevant, systematic reviews about its prevalence in animals are lacking.
Methods: We performed a systematic literature review in bibliographic databases to assess the prevalence of H5N1 in animals. A meta-analysis with a random-effects model was performed to calculate the pooled prevalence and 95 % confidence intervals (95%CI). In addition, measures of heterogeneity (Cochran's Q statistic and I^2 test) were reported.
Results: The literature search yielded 1359 articles, of which 33 studies were fully valid for analysis, including 96,909 animals. The pooled prevalence for H5N1 in birds (n = 90,045, 24 studies) was 5.0 % (95%CI: 4.0–6.0 %; $I^2 = 99.21$); in pigs (n = 3,178, 4 studies) was 1.0 % (95%CI: 0.0–1.0 %); in cats (n = 2,911, 4 studies) was 0.0 % (95%CI: 0.0–1.0 %); and in dogs (n = 479, 3 studies) was 0.0 % (95%CI: 0.0–2.0 %).
Conclusions: While the occurrence of H5N1 in animals might be comparatively limited compared to other influenza viruses, its impact on public health can be substantial when it transmits to humans. This virus can potentially induce severe illness and has been linked to previous outbreaks. Therefore, it is essential to closely monitor and comprehend the factors influencing the prevalence of H5N1 in both avian and human populations to develop effective disease control and prevention strategies.

1. Introduction

The family Orthomyxoviridae encompasses highly pathogenic avian influenza viruses comprising approximately eight genetic segments encoding proteins, categorised into different subtypes. Currently, there are 16 subtypes of hemagglutinin (H) and nine subtypes of neuraminidase (N) observed in various bird species [1–3] (see Table 1).

Over the past century, highly pathogenic avian influenza has spawned diverse outbreaks caused by distinct H5 viruses in over eight countries. The inaugural outbreak was attributed to the H5N1 strain of the AI virus in Scottish chickens in 1959 [4,5].

Waterfowl serve as the primary natural reservoir for influenza viruses, with infections in mammals, particularly pigs, originating from avian sources. Cross-species transmission can occur through genetic

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rearrangement, creating novel viruses capable of infecting different mammals. Direct spread and subsequent adaptation are also plausible [6,7].

The species barrier between birds and mammals makes viral adaptation imperative for successful replication and transmission in mammals [8]. Airborne transmission of highly pathogenic avian influenza (HPAI) between mammals necessitates efficient binding of hemagglutinin glycoprotein, receptors, and mutations [9]. Stable proteins in the mammalian respiratory tract, hemagglutinin mutations optimising viral and endosomal membrane fusion, and subsequent viral genome release into the cytoplasm are essential requirements [10].

Avian influenza virus pathogens continuously pose challenges to animal and human health. The dynamic nature of AI viruses suggests that the emergence of a pandemic-causing virus makes isolation an unlikely containment measure [11].

This study aimed to ascertain the collective occurrence of the H5N1 influenza virus in animals by conducting a systematic review accompanied by meta-analysis.

2. Methods

The drafting process follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [12].

2.1. Information sources and search strategy

A bibliographic search was carried out for studies that evaluated the prevalence of H5N1 in animals, including birds, mammals and fishes. This search used five databases: Scopus, Web of Sciences, PubMed, OVID Medline, and EMBASE. The PRESS Checklist (Peer Review of Electronic Search Strategies) was used to develop the search strategy. No restrictions were made regarding the language of the study. Literature was

Table 1
Characteristics of the included studies.

Author	Year	Country	Data collection date	Animals	Detection Method	Type of sample	n (+)	No. total samples
Mahardika G et al.	2018	Indonesia	2005-2006	Birds	Hemagglutination inhibition assay	Serum and cloacal swabs	25	6084
				Pigs		Nasal and pharyngeal swabs	11	1786
				Cats			2	108
				Dogs			3	40
El-Sayed A et al.	2013	Egypt	2013	Cattle	ELISA	Serum Samples	0	50
				Buffaloes			0	50
				Horses			36	160
				Donkeys			11	36
Nguyen D et al.	2014	Vietnam	2011–2013	Birds	RT-PCR	Oropharyngeal swabs	387	531
Marschall J et al.	2008	Germany	2006-2007	Cats	RT-PCR	Pharyngeal swabs	0	171
Bi Y et al.	2016	China	2014–2016	Birds	Hemagglutination inhibition assay	Oropharyngeal and cloacal swab	65	5552
Negovetich N et al.	2011	Bangladesh	2008–2010	Birds	Hemagglutination inhibition assay	Oropharyngeal and cloacal swab	4	1176
Pawar S et al.	2012	India	2009–2011	Birds	Hemagglutination inhibition assay	Serum, pharyngeal and cloacal swabs	5	227
Ellis T et al.	2004	Hong Kong	2002	Birds	Hemagglutination inhibition assay	Serum and cloacal swabs	79	164
Kou Z et al.	2009	China	2004–2007	Birds	RT-PCR	Cloacal swabs	149	14472
ElMasry I et al.	2017	Egypt	2009–2014	Birds	RT-PCR	Tracheal and cloacal swabs	153	4134
Oluwayelu D et al.	2011	Nigeria	2010	Dogs	Hemagglutination inhibition assay	Serum Samples	0	162
Susanti R et al. (A)	2008	Indonesia	2008	Birds	RT-PCR	Cloacal swabs	21	460
Susanti R et al. (B)	2015	Indonesia	2015	Birds	Hemagglutination inhibition assay	Cloacal swabs	4	55
Horm SV et al.	2016	Cambodia	2013	Birds	RT-PCR	Tracheal and cloacal swabs	19	24
Nidom C et al.	2012	Indonesia	2010	Birds	Hemagglutination inhibition assay	Tracheal and cloacal swabs	8	1607
Stoops A et al.	2009	Indonesia	2006–2007	Birds	RT-PCR	Serum, pharyngeal and cloacal swabs	7	1655
Keawcharoen J et al.	2011	Thailand	2004–2007	Birds	RT-PCR	Tracheal and cloacal swabs	192	24712
Nagy A et al.	2007	Czech Republic	2006	Birds	RT-PCR	Organ tissues and cloacal swabs	12	2101
El-Zoghby E et al.	2013	Egypt	2009–2010	Birds	RT-PCR	Tracheal and cloacal swabs	23	22024
Durosinlorun A et al.	2010	Nigeria	2007-2008	Birds	Hemagglutination inhibition assay	Serum Sample	110	605
Olatoye O et al.	2009	Nigeria	NR	Pigs	ELISA	Pharyngeal and cloacal swab	0	25
Goletić T et al.	2010	Bosnia	2005-2006	Birds	RT-PCR	Organ tissues, oropharyngeal and cloacal swabs	2	394
Sartika Y et al.	2018	Indonesia	2018	Birds	Hemagglutination inhibition assay	Serum Sample	7	50
Lee D et al.	2011	South Korea	2010-2011	Birds	RT-PCR	Oropharyngeal and cloacal swab	14	728
Zaman A et al.	2019	Pakistan	NR	Birds	Hemagglutination inhibition assay	Serum Sample	243	400
Monamele C et al.	2019	Cameroon	2016	Birds	RT-PCR	Nasopharyngeal and oral swabs	34	147
Yuniati G et al.	2021	Indonesia	NR	Birds	RT-PCR	Serum, pharyngeal and cloacal swabs	11	1398
Lebarbenchon C et al.	2007	France	2005-2006	Birds	RT-PCR	Cloacal swabs	0	1345
Rith S et al.	2012	Cambodia	2006–2010	Pigs	RT-PCR	Serum Sample	0	1147
Meseko C et al.	2012	Nigeria	2008	Pigs	Hemagglutination inhibition assay	Serum Sample	0	220
Zhao F-R et al.	2015	China	2010-2011	Cats	RT-PCR	Serum Samples and nasal swabs	2	1020
Hasiri A et al.	2013	Iran	NR	Dogs	Hemagglutination inhibition assay	Serum Sample	0	209
Sun L et al.	2014	China	2009–2011	Cats	Hemagglutination inhibition assay	Serum Samples and nasal swabs	1	1680
Gamarra-Toledo et al.	2023	Peru	2023	Sea Lions	Necropsy, clinical and epidemiological correlation	Lungs, Brains	1	5224
Ulloa et al.	2023	Chile	2023	Sea Lions	Immunohistochemistry (IHC) and real-time PCR	Tracheal/rectal swab pools	21	168

NR: Not Reported; RT-PCR: Real-time reverse transcription–polymerase chain reaction.

searched from the databases' inception to May 28, 2024. The complete search strategy can be found attached in Supplementary Table S1.

2.2. Study selection and data extraction

The present study included studies that evaluated the prevalence of H5N1 in animals. We only included observational studies. We excluded systematic reviews, case reports, scoping reviews, narrative reviews, and letters to the editor.

All articles found through the search strategy were uploaded to the Rayyan QCRI data management software. Here, the detection and elimination of duplicate articles was carried out. Subsequently, the articles were screened based on title/abstract, and the entire text selection was performed. Articles not meeting the selection criteria were excluded from this systematic review. All screening processes were carried out independently by four reviewers. Any discrepancies were resolved by reaching a consensus among all authors. The information from the provided articles was obtained using a data extraction template created in Microsoft Excel. We recorded the following information: author, year of publication, country, detection method, study population, number of animals with H5N1 infection.

2.3. Risk of bias assessment

The included articles' bias risk was assessed using the Newcastle-Ottawa for cross-sectional studies [13]. A score of seven stars or above on either scale denoted a low risk of bias, whereas a score of six stars or less denoted a high risk of bias. The evaluation was done independently by two reviewers.

2.4. Publication bias assessment

According to the most recent research, studies performing a proportional meta-analysis should not assess publication bias. Conventional techniques like funnel plots and Egger's test are unreliable for these investigations. This is because funnel plots were created with the presumption that research with favourable results was published more frequently than unfavourable ones. When studying and performing a quantitative analysis of prevalence, there is no consensus on what constitutes a positive result. Furthermore, no evidence suggests that proportions adjust appropriately with these tests [14,15].

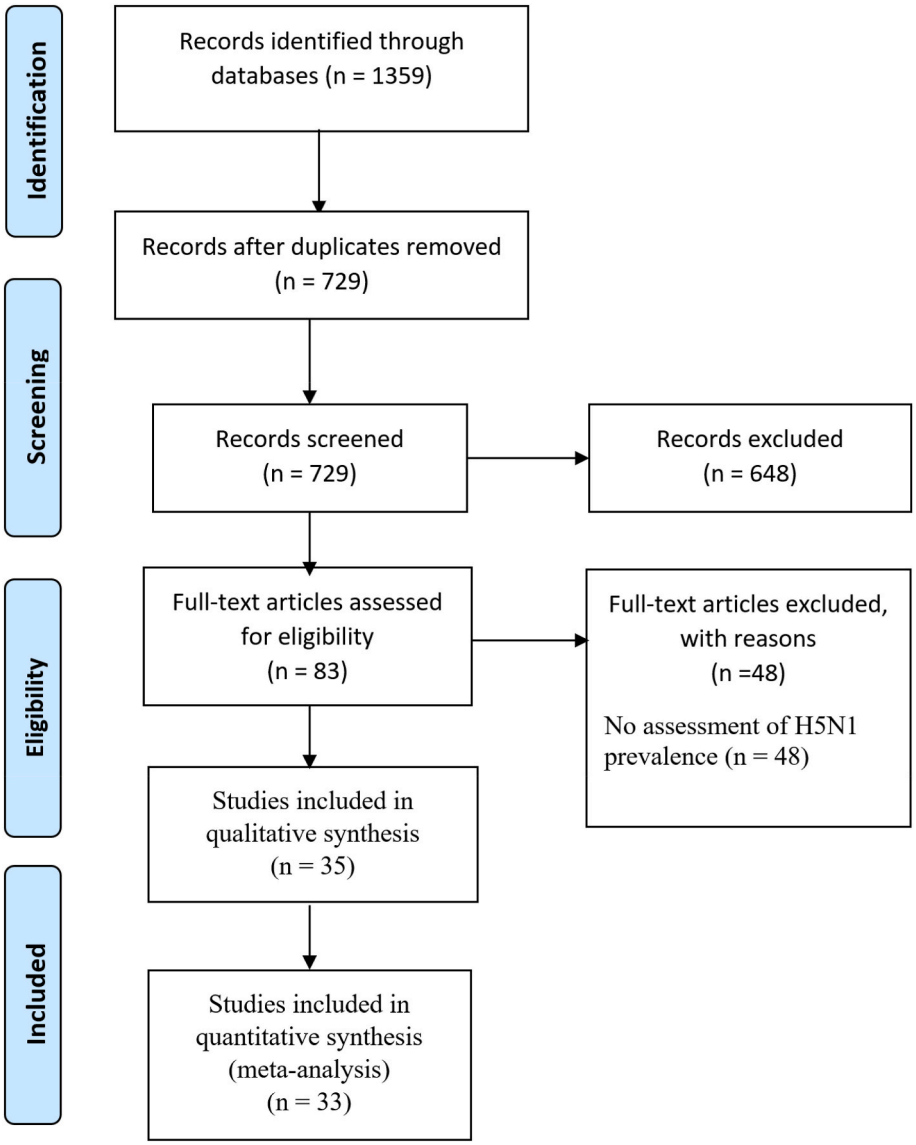

Fig. 1. PRISMA Flow diagram of studies assessed and included.

2.5. Statistical analysis

The quantitative synthesis of the results was carried out in the statistical analysis program Stata v.16®. A random effects model (Dersimonian and Laird) was used for the meta-analysis. The 95 % confidence intervals were calculated using the Clopper-Pearson method. The Freeman-Tukey Double Arcsine Transformation was used as a variance stabiliser. We used Cochran's Q test and the I2 statistic to assess the between-study heterogeneity. I2 values of 60 % or greater were categorised as severe heterogeneity; in Cochran's Q test, heterogeneity was indicated by p-values$<$0.05. Subgroup analyses were carried out using the assay method and world regions. A sensitivity analysis was performed, excluding studies with a high risk of bias.

3. Results

3.1. Study selection and studies characteristics

The systematic search identified 1359 articles, and 729 studies remained after removing duplicates. According to titles and abstracts, 648 studies were excluded from the screening. In turn, screening by full-text left 33 studies with all eligibility criteria Table 1 [16–48]. The flowchart of the selection process is shown in Fig. 1.

Thirty-three cross-sectional studies were included, with a total of 96,909 animals. The assay methods used to evaluate the presence of H5N1 were hemagglutination inhibition assay (HIA), enzyme-linked immunosorbent assay (ELISA) and real-time reverse transcription-polymerase chain reaction (RT-PCR). We only found studies conducted in Europe and Asia, with Indonesia being the country with the most significant number of studies included (7 studies). It was impossible to perform a meta-analysis of the prevalence of H5N1 in buffaloes, horses, donkeys and cattle because they were only evaluated in one study.

In the quality assessment, we found that 28 studies had a low risk of bias, and five had a high risk of bias (Supplementary Table S2).

3.2. Prevalence of H5N1 in birds

In 24 studies (n = 90,045), we found that the prevalence of H5N1 in birds was 5.0 % (95%CI: 4.0–6.0 %; $I^2 = 99.21$) (Fig. 2). In the subgroup of studies that evaluated birds with HIA (Supplementary Fig. S1), the prevalence of H5N1 was 9.0 % (95%CI: 8.0–11.0 %), and in the case of the studies that evaluated birds with RT-PCR (Supplementary Fig. S2), there was a prevalence of 4.0 % (95%CI: 3.0–5.0 %). In subgroup analyses of studies conducted in Asia (Supplementary Fig. S3), Africa (Supplementary Fig. S4) and Europe (Supplementary Fig. S5), we found a prevalence of 8.0 %, 9.0 % and 1.0 %, respectively. In the sensitivity analysis (Supplementary Fig. S6), heterogeneity remained severe with a prevalence of 4.0 % (95%CI: 3.0–5.0 %; $I^2 = 99.16$).

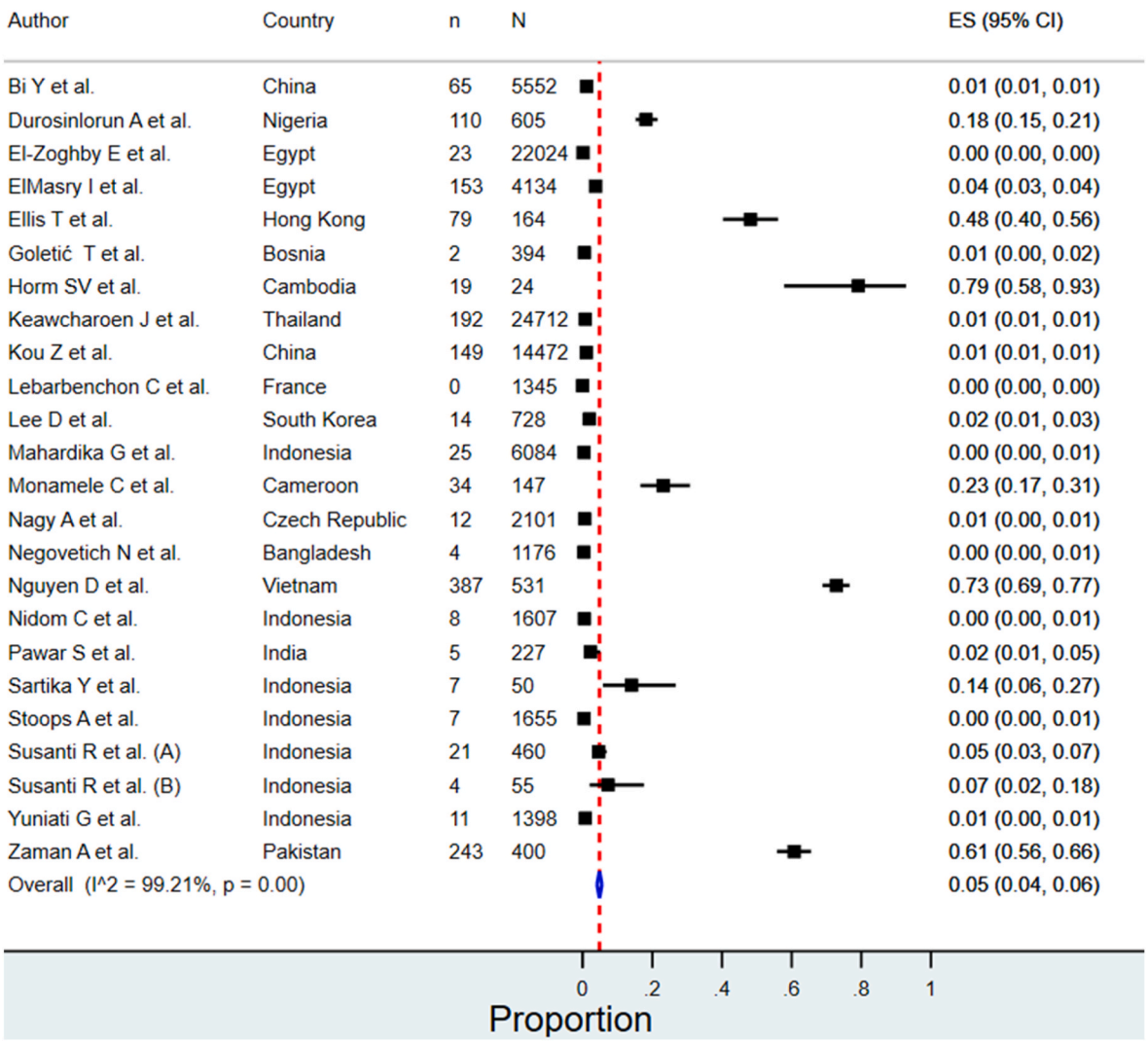

Fig. 2. Prevalence of H5N1 in birds.

3.3. Prevalence of H5N1 in pigs

In four studies (n = 3178), we found that the prevalence of H5N1 in pigs was 1.0 % (95 % CI: 0.0–1.0 %) (Fig. 3). Due to the small number of studies, subgroup analysis could not be performed. In the sensitivity analysis (Supplementary Fig. S7), no pigs were found to have the H5N1 virus.

3.4. Prevalence of H5N1 in cats

In four studies (n = 2911), we found that the prevalence of H5N1 in cats was 0.0 % (95%CI: 0.0–1.0 %) (Fig. 4). Subgroup analysis could not be performed due to the small number of studies. In the sensitivity analysis (Supplementary Fig. S8), the prevalence of 0 % was maintained.

3.5. Prevalence of H5N1 in dogs

In three studies (n = 479), we found that the prevalence of H5N1 in dogs was 0.0 % (95 % CI: 0.0–2.0 %) (Fig. 5). Due to the limited number of studies, subgroup and sensitivity analyses could not be performed.

4. Discussion

The world is facing its most significant avian flu outbreak, devastating poultry and wild bird populations [49–52]. This epidemic marks the largest in Europe, North America, and Japan, primarily driven by the H5N1 avian flu virus, clade 2.3.4.4b [53]. In 2022, infections of Highly Pathogenic Avian Influenza (HPAI) caused by H5N1 viruses from clade 2.3.4.4b resulted in the loss of over 131 million poultry across 67 countries. The disease has rapidly spread in 2023, with reported infections in 14 additional countries. As of July 12, 2023, more than 58 million poultry birds have been diagnosed with HPAI due to infections with H5N1 viruses from clade 2.3.4.4, along with slightly over 7000 wild birds in the United States alone [53]. From 2020 onwards, numerous outbreaks have been involving the clade 2.3.4.4b of HPAI viruses of the H5N1 subtype across various nations in Europe, Asia, Africa, and North America. This clade has raised significant alarm owing to its swift global spread, efficient transmission to novel bird species, and the frequent infection of diverse wild terrestrial and marine mammals, often exhibiting atypical neurotropism. Additionally, there is concern about sporadic human cases associated with this clade [54].

After including 33 studies in this systematic review with more than 96 thousand animals, the prevalence of avian influenza H5N1 was relatively low: 5 % in birds, 1 % in pigs, 0 % in cats and 0 % in dogs. In the first place, this confirms the predominant importance of H5N1 in birds and highlights the second place for mammals such as pigs. A recent report from Peru detailed a significant mortality event involving 5224 South American sea lions (*Otaria flavescens*). The incident appeared to be linked to an infection of the highly pathogenic avian influenza A(H5N1) virus [55]. A similar situation was observed in Chile. There, 169 sea lions were examined to determine their status regarding HPAIV H5N1, and the long-term stranding patterns from 2009 to 2023 were analysed. Additionally, two animals underwent necropsies. Interestingly, a notable increase in SA sea lion strandings was noted, commencing in January 2023 and reaching its peak in June 2023, with 4545 animals stranded and deceased. Significantly, this surge in mortality coincided geographically with HPAIV outbreaks affecting wild birds. Of the 168 sampled SA sea lions, 34 (20 %) tested positive for Influenza A virus, with 21 confirmed cases of HPAIV H5N1 2.3.4.4b clade in tracheal/rectal swab pools. Clinical and pathological examinations of the two necropsied stranded sea lions revealed prevalent neurological and respiratory symptoms, such as disorientation, tremors, ataxia, and paralysis, as well as acute dyspnea, tachypnea, profuse nasal secretion, and abdominal breathing—the identified lesions in necropsied animals aligned with the observed clinical signs. Confirmation of the virus through immunohistochemistry (IHC) and real-time PCR in the brain and lungs substantiated these findings [56].

AI viruses exhibit variable abilities to cause infection, disease, and mortality in different species, probably expanding its spectrum, although fortunately with low frequency as observed in this systematic review. In Peru from November 2022 to February 2023, H5N1 was identified in wild birds, poultry, and a lion (clade 2.3.4.4b) [57]. At least 24,000 sea lions died in Peru, Chile, Argentina, Uruguay, and Brazil between January and October 2023. The most plausible route of infection is cohabiting with or foraging on infected birds [58]. While wild birds typically experience asymptomatic infections, poultry transmission can result in various symptoms. Clinical signs in mammals include high fevers, respiratory distress, runny nose, neurological symptoms, oedema, and haemorrhage [3,59]. Instances such as the infection of tigers and leopards in Southeast Asia highlight the zoonotic potential of avian influenza. Limited knowledge of avian influenza in mammals necessitates ongoing research to understand airborne transmission traits [60].

The single-stranded RNA genome with a negative sense in the

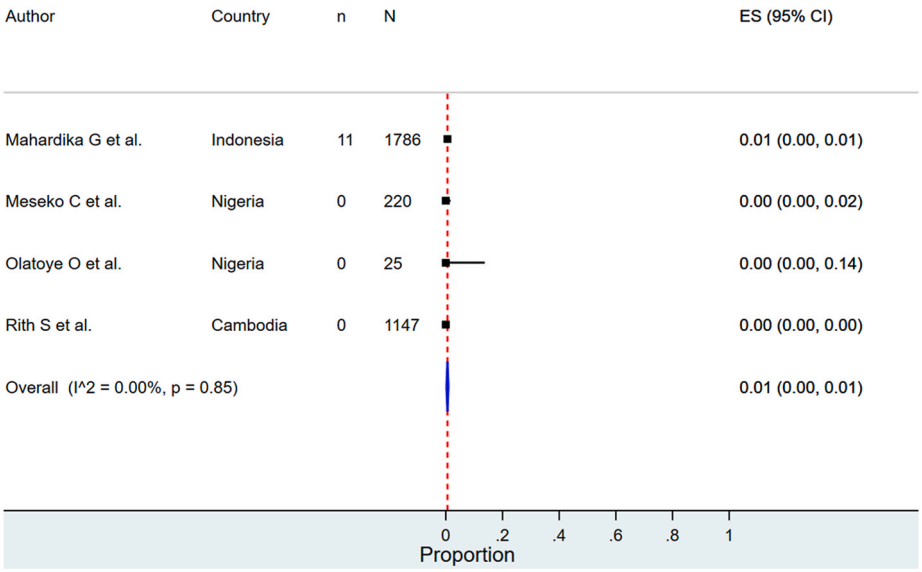

Fig. 3. Prevalence of H5N1 in pigs.

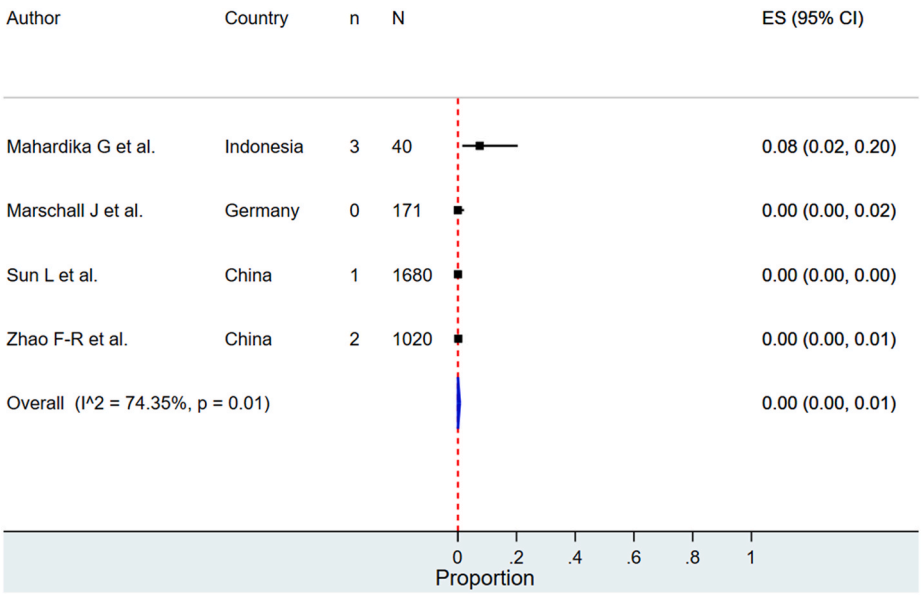

Fig. 4. Prevalence of H5N1 in cats.

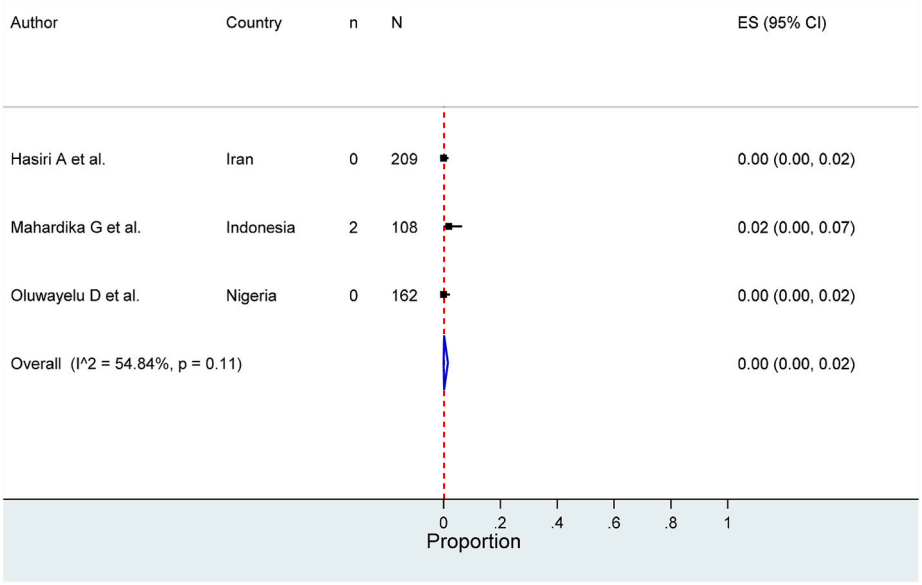

Fig. 5. Prevalence of H5N1 in dogs.

Orthomyxoviridae family can infect a broad range of animals, leading to spillover and then infecting humans. The H5N1 strain globally circulates, causing significant mortality in wild birds and poultry. Indirect H5N1 events in mammals involving symptomatic animals taken to wildlife care sites were identified in the United Kingdom and the Netherlands [61,62].

Current reports indicate escalating avian influenza cases in birds, raising zoonotic concerns. Occasional human infections with associated fatalities have been reported in approximately 23 countries since 2004. The robust survival capacity of the highly pathogenic H5N1 virus in the environment facilitates transmission through contaminated fomites, leading to potential nasopharyngeal or conjunctival inoculation [63].

Avian influenza, caused by the H5N1 virus, is predominantly considered an animal issue. Entities responsible for investigating and controlling outbreaks emphasise the need for continuous monitoring. Studies suggest the successful crossing of species barriers by rearranged H5N1 sublineages. For instance, investigating a lion's contagion in China implicated contaminated drinking water, possibly sourced from earlier supplied chickens [64,65].

The H5N1 subtype of avian influenza has garnered global attention, causing fatal infections in humans and mammals. Presently, there are no vaccines for human or animal populations specifically for H5N1. This underscores the necessity for consistent reviews to enhance epidemiological surveillance, preventive measures, and control actions against potential future pandemics resulting from interspecies transmission [66,67].

Concerns arise from unsafe practices in poultry and pig markets, potentially fostering cross-species transmission. Despite extensive environmental, medical, and biological studies, the precise conditions for interspecies transmission remain unknown, necessitating further research and development.

Several factors can influence the prevalence of H5N1 in birds and other animals. H5N1 primarily infects birds, especially waterfowl such as ducks and geese. While it can occasionally infect other species,

including mammals and humans, its natural reservoir is in wild birds [68]. H5N1 is primarily spread through direct contact with infected birds or their saliva, nasal secretions, and faeces. The virus can also be transmitted through contaminated surfaces or materials. The transmission dynamics and host specificity contribute to the relatively low prevalence in animals other than birds [69]. Influenza viruses often exhibit seasonal patterns, with increased activity during colder months. The environmental conditions can influence the survival and transmission of the virus. H5N1 may have specific ecological factors that limit its prevalence in certain seasons [70]. Wild birds, especially waterfowl, are natural reservoirs for many influenza viruses, including H5N1. These birds can carry the virus without showing signs of illness. Some birds may develop immunity after exposure to the virus, which can limit its spread within bird populations [71,72]. Influenza viruses, including H5N1, can undergo genetic changes through mutation and reassortment. This can lead to the emergence of new strains or variants. The prevalence of a specific strain may change over time due to these evolutionary processes [73–75].

More recently, an outbreak of H5N1 avian influenza in dairy cattle across several United States (US) states has raised significant concern nationally and globally; in 2024, H5N1 has been detected in dairy cattle in Texas, Kansas, Michigan, Idaho, South Dakota, New Mexico, Ohio, North Carolina and Colorado, with human case in Texas (https://www.cdc.gov/mmwr/volumes/73/wr/mm7321e1.htm). Studies are ongoing, but there is a concern regarding more human cases and even detection of H5N1 in milk and probably dairy unpasteurised products [76].

Also, in Japan, recently, a study investigated H5N1 in stranded dolphins. However, all results yielded negative. However, there was a small sample. Then, there is a need to increase research and surveillance [77].

Efforts to control and contain outbreaks of H5N1 in poultry, such as culling infected birds and implementing biosecurity measures on farms, can contribute to reducing the prevalence of the virus in domesticated bird populations [78,79].

It is important to note that while the prevalence of H5N1 in animals, as shown in this systematic review, may be relatively low compared to other influenza viruses, the virus can have significant public health implications when it infects humans, as it has the potential to cause severe illness and has been associated with outbreaks in the past [80, 81]. Monitoring and understanding the factors influencing the prevalence of H5N1 in birds and humans is crucial for effective disease control and prevention strategies [82,83]. Despite that, some experts question if avian H5N1 influenza could be the next pandemic threat of disease X [84]. It is important to highlight the importance of assessing the animal-human interface with the zoonotic implications, spillover [53], threat and pandemic potential, as observed with other viral pathogens [85].

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Ethical approval

Approval was not required.

CRediT authorship contribution statement

D. Katterine Bonilla-Aldana: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Dayana M. Calle-Hernández:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Juan R. Ulloque-Badaracco:** Writing – review & editing, Investigation, Formal analysis. **Esteban A. Alarcón-Braga:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Enrique A. Hernández-Bustamante:** Writing – review & editing, Investigation, Funding acquisition, Formal analysis, Data curation. **Juan C. Cabrera-Guzmán:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Sthephanie M. Quispe-Vasquez:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Miguel A. Huayta-Cortez:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Vicente A. Benites-Zapata:** Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Funding acquisition, Formal analysis, Data curation. **Alfonso J. Rodriguez-Morales:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

All authors report no potential conflicts.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nmni.2024.101439.

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