McMaster University | HEALTH FORUM

Living Evidence Profile

Examining what is known about the emergence, transmission and spectrum of the burden of disease of avian influenza A (H5Nx) subtypes

12 January 2024

[MHF product code: LEP 7.1]

Appendices

Appendix 1: Methodological details

We use a standard protocol for preparing living evidence profiles (LEP) to ensure that our approach to identifying research evidence is as systematic and transparent as possible in the time we were given to prepare the profile. The timing, frequency and scope of future updates of this LEP will be determined in collaboration with the requestor.

At the beginning of each LEP and throughout its development, we engage a subject matter expert who helps us to scope the question and ensure relevant context is taken into account in the summary of the evidence.

This first version of the LEP aims to identify the current state of evidence and knowledge gaps from existing evidence syntheses related to the emergence, transmission and spectrum of the burden of disease in humans of avian influenza as a first step towards informing prevention and mitigation interventions. As such, this version of the LEP was focused only on identifying existing evidence syntheses and did not include a jurisdictional scan. However, expansions in scope may be made in future versions to include single studies and/or a jurisdictional scan to provide more detailed insights to support ongoing work towards informing prevention and mitigation interventions.

Identifying research evidence

For this LEP, we searched ACCESSSS, Health Systems Evidence, Health Evidence and PubMed on 18 December 2023 using the following combination of terms: (avian influenza) OR (H5N1 or AH5N1 or A?H5N1 or H5Nx or H5N*). The searches were not limited by publication date except in PubMed, which was limited to literature published from the last five years (2019 onwards). In addition, we reviewed literature compiled from searches that were last conducted by the Public Health Agency of Canada (PHAC) on 13 December 2023. This included reviewing results from searches run by PHAC from 1 October 2022 up to the last search that was run on 13 December 2023.

These detailed search strategies are available upon request.

Each source for these documents is assigned to one team member who conducts hand searches (when a source contains a smaller number of documents) or keyword searches to identify potentially relevant documents. A final inclusion assessment is performed both by the person who did the initial screening and the lead author of the rapid evidence profile, with disagreements resolved by consensus or with the input of a third reviewer on the team. The team uses a dedicated virtual channel to discuss and iteratively refine inclusion/exclusion criteria throughout the process, which provides a running list of considerations that all members can consult during the first stages of assessment.

During this process we include evidence syntheses from published, pre-print and grey literature. We do not exclude documents based on the language of a document. However, we are not able to extract key findings from documents that are written in languages other than Chinese, English, French, Portuguese or Spanish. We provide any documents that do not have content available in these languages in an appendix containing documents excluded at the final stages of reviewing. We excluded documents that did not directly address the research questions and the relevant organizing framework.

Assessing relevance and quality of evidence

We assess the relevance of each included evidence document as being of high, moderate or low relevance to the question.

Two reviewers independently appraised the quality of the guidelines we identified as being highly relevant using AGREE II. We used three domains in the tool (stakeholder involvement, rigour of development and editorial independence) and classified guidelines as high quality if they were scored as 60% or higher across each of these domains.

Two reviewers independently appraise the methodological quality of evidence syntheses that are deemed to be highly relevant. Disagreements are resolved by consensus with a third reviewer if needed. AMSTAR rates overall methodological quality on a scale of 0 to 11, where 11/11 represents an evidence synthesis of the highest quality. High-quality evidence syntheses are those with scores of eight or higher out of a possible 11, medium-quality evidence syntheses are those with scores between four and seven, and low-quality evidence syntheses are those with scores less than four. It is important to note that the AMSTAR tool was developed to assess evidence syntheses focused on clinical interventions, so not all criteria apply to those pertaining to health-system arrangements or to economic and social responses. Where the denominator is not 11, an aspect of the tool was considered not relevant by the raters. In comparing ratings, it is therefore important to keep both parts of the score (i.e., the numerator and denominator) in mind. For example, an evidence synthesis that scores 8/8 is generally of comparable quality to another scoring 11/11; both ratings are considered 'high scores.' A high score signals that readers of the evidence synthesis can have a high level of confidence in its findings. A low score, on the other hand, does not mean that the evidence synthesis should be discarded, merely that less confidence can be placed in its findings and that the evidence synthesis needs to be examined closely to identify its limitations. (Lewin S, Oxman AD, Lavis JN, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP): 8. Deciding how much confidence to place in a systematic review. *Health Research Policy and Systems* 2009; 7 (Suppl1): S8.)

Identifying experiences from other countries and from Canadian provinces and territories

Jurisdictional scans have not been prioritized for this LEP yet. However, for future versions of this LEP we may work with the requestors and a subject matter expert to collectively decide on what countries (and/or states or provinces) to examine based on the question posed.

Preparing the profile

Each included document is cited in the reference list at the end of the LEP. For all included guidelines, evidence syntheses and single studies (when included), we prepare a small number of bullet points that provide a summary of the key findings, which are used to summarize key messages in the text. Protocols and titles/questions have their titles hyperlinked, given that findings are not yet available. We then draft a summary that highlights the key findings from all highly relevant documents (alongside their date of last search and methodological quality). Upon completion, the LEP is sent to the subject matter expert for their review.

Appendix 2: Key findings from evidence documents organized by circulating clade

Circulating subtype or clade	Biology	Epidemiology	Diagnosis	Clinical presentation	Priority populations
General H5Nx subtypes	• Most transmissions occurred at a short to medium proximity regardless of subtype or geographical location; the reproduction number for between-farm transmission was found to be between 0.03-15.7 (AMSTAR rating 6/11; literature last searched 20 September 2018) • A synthesis of avian influenza virus (H5Nx included) revealed differences in virus shedding levels among poultry, resulting from various introduction and shedding routes (large heterogeneity in methods) (AMSTAR rating 4/11; literature last searched 2017)	• Anseriformes (i.e., waterfowl) were considered the most important natural hosts and transmitters of avian influenza viruses (including H5 subtype) in China, but the prevalence of avian influenza viruses and their related antibodies in wild birds vary among regions and species (AMSTAR rating 6/11; literature last searched 20 September 2018) • Most H5N1 human infection cases from 1997 to 2019 were found in Egypt, among children and younger adults, and those with exposure to poultry (AMSTAR rating 2/9; literature last searched 31 July 2019) • Backyard farms with both swine and poultry are at risk of interspecies transmission (domestic poultry to swine) (AMSTAR rating 3/9; literature last searched 31 July 2021) • The role of backyard farms in transmission was found to be minimal, with a below-one reproduction number for between backyard farms themselves and between backyard and commercial farms (AMSTAR rating 6/11; literature last searched 20 September 2018) • Contextualizing species and virus type is important in understanding parameters of the avian influenza to obtain an accurate understanding of its transmission and risks (AMSTAR rating 5/10; literature last searched 2021) • The movement of birds, humans and fomites all play a role in transmitting	• Current surveillance methods for avian influenza viruses included sample collection from live birds at markets and farms (cloacal and tracheal/oropharyngeal swabs and blood), dead birds (swabs and/or organ samples) and environmental samples (feces, mud, water, feeding source, feathers and air and surfaces likely contaminated with viruses such as cages, chopping boards and defeathering machines); however, there was limited information on the sensitivity of the sample techniques to develop an optimal avian influenza surveillance program (AMSTAR rating 3/9; literature last searched 10 June 2019) • Surveillance and serosurveillance of the avian influenza in wild birds is important to monitor its risk of transmission to other species (AMSTAR rating 6/11; literature last searched 2021)	• H5 subtypes typically cause mild clinical symptoms among poultry but have the potential to mutate to cause severe morbidity and mortality (AMSTAR rating 6/11; literature last searched 20 September 2018)	• None identified

Circulating subtype or clade	Biology	Epidemiology	Diagnosis	Clinical presentation	Priority populations
		the avian influenza during poultry production due to cross contamination; additional research on poultry production is needed to understand transmission of this virus (AMSTAR rating 5/9; literature last searched 2019) • The 2021 prevalence of avian influenza H5N8 in birds was 1.6%, emphasizing a need for surveillance of virus transmission and migration in wildlife (AMSTAR rating 4/11; literature last searched 2021) • Between 2000 and 2019, diverse subtypes of avian influenza viruses were found in wild and domestic birds at an overall 3.0% prevalence, with H5N1 being the most frequently observed followed by H5N2 and H5N8 (AMSTAR rating 4/9; literature last searched 2019) • A high environmental viral load can facilitate indirect transmission between flocks or farms through more likely contaminated surfaces (e.g., trucks, boots) (large heterogeneity in methods) (AMSTAR rating 4/11; literature last searched 2017)	• Collection of environmental samples appear to be a promising tool given the ability to capture large samples and sequence multiple birds within a sample for the surveillance of avian influenza virus in wild waterbirds (AMSTAR rating 5/10; literature last searched 30 June 2019)		
2.3.4.4b	• None identified	• A 2020 systematic review and meta-analysis found that the overall seroprevalence of H5N1 infection among humans in China was 2.45% (862/35,159), with the seroprevalence among humans from central China (7.32%) being higher than those in other regions of China (AMSTAR rating 7/11; literature last searched 20 October 2018) • While there has been a change in recent years in primary subtypes and frequency of reports of human	• None identified	• None identified	• Serological evidence of subclinical and clinically mild avian influenza A(H5N1) infections in humans demonstrated that people with poultry exposures, such as poultry

Circulating subtype or clade	Biology	Epidemiology	Diagnosis	Clinical presentation	Priority populations
		A(HxNy) avian influenza in the Western Pacific Region (WPR), the overall public health risk from H5Nx viruses at the human-animal interface remains low (AMSTAR rating 2/9; literature last searched 31 July 2022) • H5Nx viruses of clade 2.3.4.4 were likely among wild birds in Alaska, which led to outbreaks among wild and domestic birds in Canada and the United States (AMSTAR rating 4/10; literature last searched February 2022)			workers and cullers, experienced relatively higher seroprevalence of A(H5N1) antibodies than non-poultry-exposed people; very low frequencies of antibodies were detected among close contacts of confirmed A(H5N1) cases (AMSTAR rating 3/11; literature last searched 1 September 2020)
2.3.2.1c	• None identified	• While there has been a change in recent years in primary subtypes and frequency of reports of human A(H5Nx) avian influenza in the Western Pacific Region (WPR), the overall public health risk from HxNy viruses at the human-animal interface remains low (AMSTAR rating 2/9; literature last searched 31 July 2022)	• None identified	• None identified	• None identified

Appendix 3: Key findings from evidence documents, organized by document type, and sorted by relevance

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
• Biology o Virological characteristics ▪ Infectivity/transmission • Epidemiology o Route of transmission ▪ Environmental viral load o Reported cases and other epidemiological indicators of avian influenza A(H5Nx) • Susceptibility and transmission parameters o Infectious period	H5 subtypes typically cause mild clinical symptoms among poultry but have the potential to mutate to cause severe morbidity and mortality, with most transmissions occurring at a short to medium proximity regardless of subtype or geographical location • Highly pathogenic avian influenza H5Nx caused mass mortality in wild birds and poultry. o The infectious duration at the level of the farm was estimated to be an average of 6.4-17.22 days. o The reproduction number Rh for between-farm transmission was found to be 0.03–15.7. o Most transmissions were found to occur at a short to medium proximity regardless of the subtype or geographical location. o The role of backyard farms in transmission was found to be minimal, with a below-one reproduction number for between backyard farms themselves and between backyard and commercial farms.	High	No	3/9	2023	No	No
• Biology o Circulating clades ▪ 2.3.4.4b ▪ 2.3.2.1c ▪ Other (if new subtypes identified as having emerged) o Genomic changes and impacts on: ▪ Infectivity/transmission • Epidemiology (including transmission) o Route of transmission ▪ Bird/non-human mammal to human o Reported cases and other epidemiological indicators of avian influenza A(H5Nx)	While there has been a change in recent years in primary subtypes and frequency of reports of human A(HxNy) avian influenza in the Western Pacific Region (WPR), the overall public health risk from HxNy viruses at the human-animal interface remains low • Between 1 October 2017 to 31 July 2022 in the WPR, there was a reduction of A(H7N9) and A(H5N1), and an increase of A(H5N6) and A(H9N2), with three new subtypes, A(H7N4), A(H10N3) and A(H3N8), being reported from China during that time period. • Infections were almost exclusively associated with human contact with infected birds.	High	No	2/9	31 July 2022	No	No

• Biology o Circulating clades ▪ 2.3.4.4b o Virological characteristics ▪ Virulence/disease severity • Epidemiology (including transmission) o Route of transmission ▪ Bird/non-human mammal to human (i.e., zoonotic transmission) ▪ Environmental viral load (e.g., avian and mammalian viral shedding) ▪ Human to human o Reported cases and other epidemiological indicators of avian influenza A(H5Nx) • Diagnosis o Serological diagnostics • Clinical presentation o Immunological characteristics ▪ Antigen/antibody and cellular immune responses • Priority populations o Groups at higher risk of exposure ▪ Working on a commercial poultry farm ▪ Breeding and handling birds ▪ Working with live or recently killed poultry ▪ Working with wild birds and/or mammals for healthcare, research and conservation ▪ Working or visiting live bird or mammal markets	Serological evidence of subclinical and clinically mild avian influenza A(H5N1) infections in humans demonstrated that people with poultry exposures, such as poultry workers and cullers, experienced relatively higher seroprevalence of A(H5N1) antibodies than non-poultry-exposed people; very low frequencies of antibodies were detected among close contacts of confirmed A(H5N1) cases • The mean seroprevalence was 0.2, 0.6, and 1.8% for poultry workers, poultry cullers, and persons with both poultry and human exposures, respectively, across studies that utilized the WHO seropositivity criteria; the mean seroprevalence was 0% among the general population and close contacts of confirmed A(H5N1) cases. • Seroprevalence was also higher in persons exposed to A(H5N1) clade 0 virus than in participants exposed to other clades of A(H5N1) virus. • Among occupationally exposed populations, people who worked in live poultry markets had higher frequencies of A(H5N1) virus-specific antibodies than poultry farmers and veterinarians.	High	No	3/11	1 September 2020	No	None identified

▪ Working in healthcare settings and other contacts of cases							
• Epidemiology (including transmission) ○ Route of transmission ▪ Bird to non-human mammal ○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)	Between 2000 and 2019, diverse subtypes of avian influenza viruses were found in wild and domestic birds in sub-Saharan Africa at an overall 3.0% prevalence, with H5N1 being the most frequently observed followed by H5N2 and H5N8 • There is a higher prevalence of avian influenza virus in sub-Saharan Africa during the dry season when Eurasian migratory birds are present in low numbers; a possible explanation for this may be due to an increased waterfowl clustering resulting from fewer bodies of water (this seasonality was found to be statistically insignificant). • Indigenous African bird species and migratory waterbirds from Eurasia keep avian influenza viruses in circulation. • A detection of H5 avian influenza viruses in both wild and domestic birds suggests the possibility of transmission between the two • High pathogenicity avian influenza viruses were more frequently found in domestic birds, particularly in chickens and ducks. • H5N1 high pathogenicity avian influenza viruses were found to be widespread in West Africa, which may be due to this region being a major wintering destination for migratory waterbirds. • The continued circulation of H5N1 high pathogenicity avian influenza viruses may be due to factors including: ○ unlawful transportation of infected poultry (sometimes crossing national borders) ○ farming of multiple livestock species ○ low adherence to biosecurity measures in bird markets. • H5N8 high pathogenicity avian influenza infection was first detected in Egypt and Nigeria at around the same time. • H5N2 high pathogenicity avian influenza viruses have caused outbreaks in South African ostrich farms.	High	No	4/9	2019	No	None identified

• Epidemiology (including transmission) o Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution) • Diagnosis o Molecular methods for rapid detection	Current surveillance methods for avian influenza viruses included sample collection from live birds at markets and farms (cloacal and tracheal/oropharyngeal swabs and blood), dead birds (swabs and/or organ samples) and environmental samples (feces, mud, water, feeding source, feathers and air and surfaces likely contaminated with viruses such as cages, chopping boards and defeathering machines); however, there was limited information on the sensitivity of the sample techniques to develop an optimal avian influenza surveillance program • There are limited studies that focused on the sensitivity of environmental sample techniques with variations according to prevalence, subtype, species, age, density of birds sampled, collection, sample handling and testing methods. • There is limited information on the optimal avian influenza surveillance programs due to lack of standardized protocols and methods in the literature.	High	No	3/9	10 June 2019	No	None identified
• Epidemiology (including transmission) o Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution) • Diagnosis o Molecular methods for rapid detection	Collection of environmental samples appear to be a promising tool given the ability to capture large samples and sequence multiple birds within a sample for the surveillance of avian influenza virus in wild waterbirds • Sequencing can be done either on isolates or directly through an environmental sample; virus isolation was most common with water samples, allowing for identifying specific viral strains. • Environmental samples were well-suited for surveillance of avian influenza viruses in wild waterbirds, as they provide information on multiple birds or species within a sample, allowing for large samples to be easily collected.	High	No	5/10	30 January 2019	No	None identified
• Biology o Circulating clades ▪ 2.3.4.4b o Virological characteristics ▪ Infectivity/transmission o Reported cases and other epidemiological indicators of avian influenza A(H5Nx)	A 2020 systematic review and meta-analysis found that the overall seroprevalence of H5N1 infection among humans in China was 2.45% (862/35,159), with the seroprevalence among humans from central China (7.32%) being higher than those in other regions of China. • In all 56 included studies, the seroprevalence detected by haemagglutination inhibition (HI)	High	No	7/11	20 October 2018	No	None identified

• Diagnosis ○ Molecular methods for rapid detection Serological diagnostics	tests and microneutralization test (MNT) was 1.30% and 4.37%, respectively. • Due to its large scale of poultry production and the location of three migratory bird fly-aways, China is recognized as a geographical area with suitable conditions for the emergence of novel influenza viruses.						
• Epidemiology (including transmission) ○ Route of transmission ▪ Bird to non-human mammal ▪ Bird/non-human mammal to human (i.e., zoonotic transmission)	Anseriformes (i.e., waterfowl) were considered the most important natural hosts and transmitters of avian influenza viruses (including H5 subtype) in China, but the prevalence of avian influenza viruses and their related antibodies in wild birds vary among regions and species • Using serological methods or reverse transcription-polymerase chain reaction (RT-PCR) to study avian influenza viruses and their antibodies among wild birds appeared to be costly but were most sensitive to detecting infections, whereas collecting eggs from wild birds appeared to be easier as egg yolks contained appropriate materials for monitoring the prevalence of avian influenza viruses. • Anseriformes (i.e., waterfowl) were considered the most important natural hosts and transmitters of avian influenza viruses. • There was evidence to raise concern about potential transmission of H5 subtypes from mutations in wild birds to poultry or humans. • The prevalence of H5 subtype in China was 0.6% with estimated avian influenza virus antibodies of 12.3%.	High	No	6/11	20 September 2018	No	None identified
• Epidemiology (including transmission) ○ Route of transmission ▪ Bird/non-human mammal to human (i.e., zoonotic transmission) ▪ Human to human ○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)	Most H5N1 human infection cases from 1997 to 2019 were found in Egypt, among children and younger adults, and those with exposure to poultry • H5N1 human infections had a case fatality risk of 52.4% among laboratory-confirmed cases reported between 1997 to 2019. • Human infections with H5N1 and H5N6 were reported between 2014 and 2015 in China and Egypt. • According to WHO documents and the literature, H5N1 human infections were reported between 1997 to 2019, with a case fatality risk of 52.4% among laboratory-confirmed cases.	High	No	2/9	31 July 2019	No	None identified

	○ Most cases were reported in Egypt, followed by Indonesia, Vietnam, Cambodia and mainland China. ○ A seasonal peak in the winter was detected among these countries. ○ Most of the cases were found among children and younger adults, with a higher proportion of women in Southeast Asia and China. ○ 97.4% were linked to poultry exposure, suggesting limited human-to-human transmission. • Other subtypes like H5N6 were linked with causing deaths. • One report indicated that a woman from the same family with reported H5N1 cases was confirmed as a human-to-human transmission.						
• Epidemiology (including transmission) ○ Route of transmission ▪ Bird to non-human mammal	Backyard farms with both swine and poultry are at risk of interspecies transmission (domestic poultry to swine) • The large numbers of H5N1 viruses may be due to migratory wild birds from the East Africa–West Asia flyway, and may potentially lead to interactions with swine, poultry and wild birds in backyard farms.	High	No	3/9	31 July 2021	No	None identified
• Epidemiology ○ Route of transmission ▪ Bird to non-human mammal ○ Reported cases and other epidemiological indictors of avian influenza ○ Susceptibility and transmission parameters ▪ Latent period ▪ Infectious period	Contextualizing species and virus type is important in understanding parameters of the avian influenza to obtain an accurate understanding of its transmission and risks • The purpose of this review was to review and assess variation of available data for the avian influenza related to reproductive number, infectious period, species type, virus type and pathogenicity. • The most common types of the virus researched where H5N1 and H7N3. • The mean infectious period ranged from 6.2 to 7.7 days, with a possible latency period of one day. ○ The confidence in this estimate is low due to challenges with measuring at a flock level. • Wild ducks were more likely to be exposed to the virus than other bird species, suggesting that wildlife may be more affected.	High	No	5/10	2021	Not available	None identified

	• Transmission was more likely to occur within flocks than between. • No significant differences were identified for pathogenicity across studies. • The authors concluded by noting the variability in estimates across studies, emphasizing the importance of contextualizing results.						
• Epidemiology ○ Route of transmission ▪ Bird to non-human mammal • Priority populations ○ Groups at higher risk of exposure ▪ Working on a commercial poultry farm	The movement of birds, humans and fomites all play a role in transmitting the avian influenza during poultry production due to cross contamination; additional research on poultry production is needed to understand transmission of this virus • The purpose of this scoping review was to identify the routes of transmission of avian influenza in poultry production to improve the understanding of the roles animals and humans play on the spread of the virus. • Many sources included in this review described transmission of the virus through wildlife birds to commercial farms and production networks. • Transmission across may occur due to cross contamination during transportation of poultry and eggs. ○ Poultry farm industry practices like bird pickup networks, inefficient feed deliveries, live movement between farms, and uncleaned egg transports may increase the spread of transmission. ○ Fomite can participate in transmission, particularly during the layer production of egg transport and bird pickup. ○ Human movements in poultry production including part-time workers, movement of veterinarians with products, or central farm networks are also likely to spread the virus. • The role of humans and fomites in trade networks could not be identified.	High	No	5/9	2019	Not available	• Occupation
• Biology ○ Virological characteristics ▪ Infectivity/transmission ▪ Pathogenicity • Epidemiology ○ Route of transmission	A synthesis of avian influenza virus (H5Nx included) revealed differences in virus shedding levels among poultry, resulting from various introduction and shedding routes (large heterogeneity in methods) • In all poultry species, high pathogenicity avian influenza virus shedding was found to be	High	No	4/11	2017	Not available	None identified

▪ Environmental viral load ○ Susceptibility and transmission parameters ○ Virus shedding	higher than that of low pathogenicity avian influenza virus. • A high environmental viral load can facilitate indirect transmission between flocks or farms through more likely contaminated surfaces (e.g., trucks, boots). • For the introduction routes of high pathogenicity avian influenza viruses, intranasal or intraconal routes resulted in no difference in shedding compared to infection by contact. • For the introduction routes of low pathogenicity avian influenza viruses, aerosol, intranasal and oropharyngeal routes resulted in greater shedding compared to infection by contact. • For high pathogenicity avian influenza viruses: ○ respiratory shedding was higher than cloacal shedding ○ higher shedding through the respiratory tract was observed in ducks than in chickens ○ lower shedding through the cloaca was observed in ducks than in chickens. • For low pathogenicity avian influenza viruses: ○ similar shedding through the respiratory and digestive tracts was seen in ducks and chickens ○ higher shedding through the cloaca was observed in ducks than in chickens ○ higher shedding through the cloaca was observed in turkeys than in chickens. • It is more likely for low pathogenicity avian influenza virus to spread among a turkey flock than a chicken flock. • Within a chicken flock, there is a high chance an infection will <u>not</u> be widespread when the avian influenza virus comes from a different order (high or low pathogenicity). • Within a turkey flock, there is a high chance an infection will be widespread when the avian influenza virus comes from a different order (high or low pathogenicity).						
• Epidemiology ○ Route of transmission	Surveillance and serosurveillance of the avian influenza in wild birds is important to monitor its risk of transmission to other species	Medium	No	6/11	2021	Not available	None identified

▪ Bird to non-human mammal ○ Reported cases and other epidemiological indictors of avian influenza • Diagnosis ○ Serological diagnostics (e.g., self-testing, point-of-care diagnostics)	• The purpose of this systematic review was to estimate the prevalence of avian influenza in wild birds located in South Korea. • This study reported that the prevalence of avian influenza was approximately 2%, indicating that 2% of wild birds in South Korea were carrying the virus. The seroprevalence was 16%, suggesting 16% of wild birds may have been exposed to it. • This study suggests that surveillance measures are needed to monitor transmission across species.						
• Epidemiology ○ Route of transmission ▪ Bird to non-human mammal ○ Reported cases and other epidemiological indictors of avian influenza	The 2021 prevalence of avian influenza in birds was 1.6%, emphasizing a need for surveillance of virus transmission and migration in wildlife • The purpose of this systematic review was to estimate the prevalence of avian influenza in birds. • This study reported that the prevalence of the avian influenza was 1.6%. • This study emphasizes the need for additional surveillance of bird habits, poultry systems and migration routes to monitor the transmission of the avian influenza.	Medium	No	4/11	2021	Not available	None identified
• Biology ○ Circulating clades ▪ 2.3.4.4b ▪ Other (if new subtypes identified as having emerged) • Epidemiology (including transmission) ○ Route of transmission ▪ Bird to non-human mammal ▪ Non-human mammal to mammal ▪ Environmental viral load • Diagnosis ○ Serological diagnostics (e.g., self-testing, point-of-care diagnostics)	H5Nx viruses of clade 2.3.4.4 were likely among wild birds in Alaska, which led to outbreaks among wild and domestic birds in Canada and the United States • H13, H16, H1 and H9 subtypes were commonly identified in gull species and H3, H4 and H5 subtypes were more commonly found in duck species. • Seroprevalence rates of all subtypes including H5 were generally found to be much higher than viral shedding, reflecting exposure throughout the lifecycle.	Medium	No	4/10	February 2022	No	None identified

Appendix 4: Documents excluded at the final stages of reviewing

Document type	Hyperlinked title
Evidence syntheses	Antivirals for influenza in healthy adults: Systematic review
	Comparative effectiveness of H7N9 vaccines in healthy individuals
	Efficacy of avian influenza vaccine in poultry: A meta-analysis
	Prediction of highly pathogenic avian influenza vaccine efficacy in chickens by comparison of in vitro and in vivo data: A meta-analysis and systematic review
	Serological evidence of human infection with avian influenza A(H7N9) virus: A systematic review and meta-analysis
Literature reviews with no systematic searches	A brief introduction to avian influenza virus
	A brief history of bird flu
	A comprehensive review of highly pathogenic avian influenza (HPAI) H5N1: An imminent threat at doorstep
	A global perspective on H9N2 avian influenza virus
	A literature review of the use of environmental sampling in the surveillance of avian influenza viruses
	A review of avian influenza a virus associations in synanthropic birds
	A review of H5Nx avian influenza viruses
	A review of knowledge discovery process in control and mitigation of avian influenza
	A review on current trends in the treatment of human infection with H7N9-avian influenza A
	Adenoviral vectors as vaccines for emerging avian influenza viruses
	Alarming situation of emerging H5 and H7 avian influenza and effective control strategies
	An outbreak of highly pathogenic avian influenza (H7N7) in Australia and the potential for novel influenza a viruses to emerge
	An overview of avian influenza in the context of the Australian commercial poultry industry
	Avian influenza (H5N1) virus, epidemiology and its effects on backyard poultry in Indonesia: A review
	Avian influenza A (H7N9) virus: From low pathogenic to highly pathogenic
	Avian influenza A virus associations in wild, terrestrial mammals: A review of potential synanthropic vectors to poultry facilities
	Avian influenza in the greater Mekong subregion, 2003–2018
	Avian influenza in wild birds and poultry: Dissemination pathways, monitoring methods, and virus ecology
	Avian influenza overview June–September 2023
	Avian influenza revisited: Concerns and constraints
	Avian influenza viruses at the wild–domestic bird interface in Egypt
	Avian influenza viruses in humans: Lessons from past outbreaks
	Avian influenza: Strategies to manage an outbreak
	Backyard poultry: Exploring non-intensive production systems
	Control of avian influenza in China: Strategies and lessons
	Controlling avian influenza virus in Bangladesh: Challenges and recommendations
	Emerging and re-emerging infectious diseases in the WHO Eastern Mediterranean region, 2001-2018

	Emerging and re-emerging zoonotic viral diseases in Southeast Asia: One health challenge
	Emerging diseases of avian wildlife
	Emerging HxNy influenza A viruses
	Evolution and adaptation of the avian H7N9 virus into the human host
	Evolution and current status of influenza a virus in Chile: A review
	Evolutionary pressures rendered by animal husbandry practices for avian influenza viruses to adapt to humans
	Global patterns of avian influenza A (H7): Virus evolution and zoonotic threats
	H5 influenza viruses in Egypt
	H7N9 influenza virus in China
	Highly pathogenic avian influenza in Bulgaria – A review
	Immune control of avian influenza virus infection and its vaccine development
	Immune responses to avian influenza viruses
	Influenza A virus infection in cats and dogs: A literature review in the light of the "one health" concept
	Influenza virus infections in cats
	Inventory of molecular markers affecting biological characteristics of avian influenza A viruses
Single studies	Managing the challenges of a highly pathogenic avian influenza H5N8 outbreak in Uganda: A case study
	Novel avian influenza a virus infections of humans
	Opening pandora's box at the roof of the world: Landscape, climate and avian influenza (H5N1)
	Pandemic potential of highly pathogenic avian influenza clade 2.3.4.4 a(h5) viruses
	Peering into avian influenza A(H5N8) for a framework towards pandemic preparedness
	Potential cross-species transmission of highly pathogenic avian influenza H5 subtype (HPAI H5) viruses to humans calls for the development of H5-specific and universal influenza vaccines
	Rational approach to vaccination against highly pathogenic avian influenza in Nigeria: A scientific perspective and global best practice
	Review of poultry recombinant vector vaccines
	Strategies for enhancing immunity against avian influenza virus in chickens: A review
	Synthesis and biological evaluation of benzothiazolyl-pyridine hybrids as new antiviral agents against H5N1 bird flu and SARS-COV-2 viruses
	The emergence and decennary distribution of clade 2.3.4.4 HPAI H5Nx
	The epidemiology, virology, and pathogenicity of human infections with avian influenza viruses
	The neuropathogenesis of highly pathogenic avian influenza H5Nx viruses in mammalian species including humans
	Vaccination and antiviral treatment against avian influenza H5Nx viruses: A harbinger of virus control or evolution

References

1. Calle-Hernández DM, Hoyos-Salazar V, Bonilla-Aldana DK. Prevalence of the H5N8 influenza virus in birds: Systematic review with meta-analysis. *Travel Med Infect Dis* 2023; 51: 102490.
2. Chauhan RP, Gordon ML. A systematic review of influenza A virus prevalence and transmission dynamics in backyard swine populations globally. *Porcine Health Management* 2022; 8(1): 10.
3. Chen X, Li C, Sun H-T, Ma J, Qi Y, Qin S-Y. Prevalence of avian influenza viruses and their associated antibodies in wild birds in China: A systematic review and meta-analysis. *Microbial Pathogenesis* 2019; 135: 103613.
4. Chen X, Wang W, Wang Y, et al. Serological evidence of human infections with highly pathogenic avian influenza A(H5N1) virus: a systematic review and meta-analysis. *BMC M*ed 2020; 18(1): 377.
5. Coombe M, Iwasawa S, Byers KA, et al. A systematic review and narrative synthesis of the use of environmental samples for the surveillance of avian influenza viruses in wild waterbirds. *The Journal of Wildlife Diseases* 2021; 57(1): 1-18.
6. Gass JD, Jr., Kellogg HK, Hill NJ, Puryear WB, Nutter FB, Runstadler JA. Epidemiology and Ecology of Influenza A Viruses among Wildlife in the Arctic. *Viruses* 2022; 14(7).
7. Germeraad EA, Sanders P, Hagenaars TJ, Jong MCM, Beerens N, Gonzales JL. Virus Shedding of Avian Influenza in Poultry: A Systematic Review and Meta-Analysis. *Viruses* 2019; 11(9): 812.
8. Hautefeuille C, Dauphin G, Peyre M. Knowledge and remaining gaps on the role of animal and human movements in the poultry production and trade networks in the global spread of avian influenza viruses – A scoping review. PLoS One 2020;15(3): e0230567.
9. Hood G, Roche X, Brioudes A, et al. A literature review of the use of environmental sampling in the surveillance of avian influenza viruses. *Transboundary and Emerging Diseases* 2021; 68(1): 110-26.
10. Kalonda A, Saasa N, Nkhoma P, et al. Avian influenza viruses detected in birds in Sub-Saharan Africa: A Systematic Review. *Viruses* 2020; 12(9): 993.
11. Kirkeby C, Ward MP. A review of estimated transmission parameters for the spread of avian influenza viruses. *Transboundary and Emerging Diseases* 2022; 69(6): 3238-46.
12. Lambert S, Bauzile B, Mugnier A, Durand B, Vergne T, Paul MC. A systematic review of mechanistic models used to study avian influenza virus transmission and control. *Veterinary Research* 2023; 54(1): 96.
13. Ntakiyisumba E, Lee S, Park BY, Tae HJ, Won G. Prevalence, Seroprevalence and risk factors of avian influenza in wild bird populations in Korea: A systematic review and meta-analysis. *Viruses* 2023;15(2): 472.
14. Philippon DAM, Wu P, Cowling BJ, Lau EHY. Avian influenza human infections at the human-animal interface. *The Journal of Infectious Diseases* 2020; 222(4): 528-37.
15. Qi Y, Ni HB, Chen X, Li S. Seroprevalence of highly pathogenic avian influenza (H5N1) virus infection among humans in mainland China: A systematic review and meta-analysis. *Transbound Emerg Dis* 2020; 67(5): 1861-71.
16. Skufca J, Bell L, Molino JP, et al. An epidemiological overview of human infections with HxNy avian influenza in the Western Pacific Region, 2003–2022. *Western Pacific Surveillance and Response Journal: WPSAR* 2022; 13(4): 1.

Bhuiya A, T Bain, Dass R, Chen K, Wilson MG. Living evidence profile 7.1: Examining what is known about the emergence, transmission and spectrum of the burden of disease of avian influenza A (H5Nx) subtypes. Hamilton: McMaster Health Forum, 12 January 2024.

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