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

17 July 2024

[MHF product code: LEP 7.4]
*Note that this product was previously labelled as LEP 8, but has since been changed to LEP 7 to accompany a complementary LEP (now with the product code LEP 8) about public health strategies that can be used to prevent, reduce and/or mitigate avian influenza spillover to humans.

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.

For LEP 7.4, we re-ran searches on 8 July 2024 to identify any new evidence documents in ACCESSSS, Health Systems Evidence, Health Evidence, and PubMed since the last LEP version (previous searches were conducted on 18 December 2023, 1 May 2024, and 13 May 2024). The searches used the following combination of terms: (avian influenza) OR (H5N1 or AH5N1 or A?H5N1 or H5Nx or H5N*) (limited using the search filters for reviews and systematic reviews) to identify any new evidence documents since the last search on 13 May 2024. This was supplemented with an additional search on 8 July 2024 in PubMed (which was conducted previously on 1 May and 13 May 2024) for any literature from the last five years related to bovine or ruminant related transmission using this combination of terms: (avian influenza) OR (H5N1 or AH5N1 or A?H5N1 or H5Nx or H5N*) AND (bovine OR cow OR cattle OR dairy OR ruminant). We also searched the USDA National Agricultural Library on 8 July 2024 (previously searched on 1 May 2024 and 13 May 2024 for previous versions) using the same set of terms with the first set searched in the title and the second set with synonyms for bovine search in the title or abstract. For example, we searched for anything relevant to dairy cattle, other non-human mammals (including ruminants), transmission associated with dairy products, and risk to livestock. Lastly, we searched MedRxiv and BioRxiv on 8 July 2024 for pre-print articles by combining (avian influenza OR H5N1 OR AH5N1) in the advanced search with individual searches for each of the following for any evidence documents published between 14 May 2024 to 8 July 2024: "bovine," "cattle," "dairy cattle," "cow," and "ruminant." In addition, in previous versions of the LEP, 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. Given that we originally only included evidence syntheses, we re-reviewed these searches for LEP 7.2 for any single studies relevant to bovine- or ruminant-related transmission.

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 LEP, 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 using the first version of the AMSTAR tool. Two reviewers independently appraise each synthesis, and 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 a review 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 implementation strategies. Furthermore, we apply the AMSTAR criteria to evidence syntheses addressing all types of questions, not just those addressing questions about effectiveness, and some of these evidence syntheses addressing other types of questions are syntheses of qualitative studies. While AMSTAR does not account for some of the key attributes of syntheses of qualitative studies, such as whether and how citizens and subject-matter experts were involved, researchers' competency, and how reflexivity was approached, it remains the best general quality-assessment tool of which we're aware. 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 it 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

We work with the requestors to collectively decide on what countries (and/or states or provinces) to examine based on the question posed. We hand searched government and stakeholder websites of other select countries (Australia, Brazil, Cambodia, Chile, China, Ecuador, France, New Zealand, Spain, United Kingdom (National Health Service, UK Health Security Agency, Department for Environment Food and Rural Affairs), United States (Centers for Disease Control and Prevention, United States Department of Agriculture, Food and Drug Administration), and Vietnam), international organizations (World Health Organization, Pan American Health Organization, World Organization for Animal Health, European Centre for Disease Prevention and Control, and Food and Agriculture Organization), and Canadian provinces and territories (e.g., relevant animal and human health agencies, agriculture, industry groups, sub-national research organizations) to identify any publicly available information published since 1 February 2024. For all countries and Canadian provinces and territories, we searched relevant government and stakeholder websites including national health and public health agency websites. While we do not exclude content based on language, where information is not available in English, Chinese, French, Portuguese, or Spanish, we attempt to use site-specific translation functions or Google Translate. For LEP 7.4, we searched the select countries for any relevant experiences and documents published between 14 May 2024 to 12 July 2024. A full list of websites and organizations searched is available upon request.

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	• Influenza A virus receptors found in humans, ducks, and chickens were widely expressed in the bovine mammary gland and respiratory tract, which the authors suggest helps to explain the high levels of H5N1 virus in infected bovine milk and the potential to lead to novel genomic changes in influenza A virus (Pre-print) • H5N1 influenza A virus replicated with high efficacy in precision-cut lung slices from human donors of different ages, with reduced replication among older donors compared to younger donors (Pre-print) • The evolution and host adaptation of influenza A virus (IAV) in bovine species has been hindered until the emergence of novel influenza D virus in cattle, as some bovine host factors that may have anti-influenza properties could have provided IAV resilience for bovines, but more research is needed to ascertain host-specific factors that have contributed to this differential (AMSTAR rating 1/9; literature last searched 2019) • 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	• Dairy cattle are susceptible to infection with highly pathogenic avian influenza (HPAI) H5N1 virus and can shed virus in milk and, therefore, might potentially transmit infection to other mammals via unpasteurized milk (Published June 2024) • An outbreak among Texas dairy cattle revealed the emergence of an avian influenza A(H5N1) with significant novel mutations, identified potential spillover to humans causing mild to moderate influenza-like symptoms, and highlighted the necessity for further studies on the virus's pathogenicity and transmission dynamics (Published July 2024) • Holstein dairy cows naturally infected with A(H5N1) virus showed significant viral presence in their mammary glands and milk, highlighting the virus's adaptability and potential cross-species transmission (Published July 2024) • Early monitoring for the presence of H5 RNA in milk from dairy cattle is important to prevent outbreaks of the virus and transmission of the virus to humans (Pre-print) • A surveillance study in New York showed that birds containing the A(H5N1) virus are present in urban areas; therefore, urban based surveillance programs are essential to monitor the spread of the A(H5N1) virus at the animal-human interface (Published 15 June 2024) • A geospatial and exposure analysis found that non-waterfowl species had the highest dairy farm exposure, with other factors (i.e., livestock trade, poultry litter feed, contaminated milking machinery) also contributed to the amplification of	• 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)	• According to a single study of surveillance data, the risk of infection of avian influence A(H5) for the general population in Europe is low, but higher for those exposed to infected animals (Published 2024)

Circulating subtype or clade	Biology	Epidemiology	Diagnosis	Clinical presentation	Priority populations
	(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)	the outbreaks in the United States (Pre-print) • The ongoing H5N1 panzootic event has significantly impacted biodiversity and mammalian health due to multiple factors (e.g., broader geographic impact, increased number of infected mammal species, potential for mammal-to-mammal transmission), highlighting the importance of continuous surveillance and international collaboration (AMSTAR rating 4/9; literature last searched 2023) • All reported cases of H5N6 in humans had prior contact with birds and were found to have a high disease severity, with 95% of cases resulting in hospitalization (AMSTAR rating 4/9; literature last searched 2021) • 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	• 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)		

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		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 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) • A single study found that human infections of avian influenza A(H5) remained rare between December 2023 and March 2024 and Europe and North America continued to see widespread outbreaks in domestic and wild birds; goat kids in the U.S. found infected with			

Circulating subtype or clade	Biology	Epidemiology	Diagnosis	Clinical presentation	Priority populations
		influenza A(H5N1) virus represented the first natural infection in any ruminant species worldwide (Published 2024) • Cow-to-cow transmission of H5N1 was reported in dairy cattle in the U.S., with cows experiencing apparent systemic illness, an abrupt drop in milk production, reduced feed intake and rumination, abundant virus shedding, and the production of thick, creamy yellow milk (Published March 2024) • Wild waterfowl act as a potential transmission pathway for avian influenza to livestock on commercial facilities, and small or isolated natural and artificial water or food sources in or near livestock facilities increase the likelihood of attracting these birds (Published January 2022)			
2.3.4.4b	• An experimental study discovered that European HPAI A(H5N1) has the ability to cause infection and proliferate in bovine epithelial cells, similar to the North American lineage HPAI A(H5N1) (Published 26 June 2024) • The circulation of clade 2.3.4.4b B3.13 virus among dairy cattle poses a potential zoonotic threat, requiring continued monitoring to inform epidemiological risk and early warning for any interspecies transmission (Pre-print) • Given the significant presence of influenza A viruses in various water matrices associated with poultry (prevalence rates ranging from 4.3% to 76.4%) and wild bird habitats	• The H5N1 avian flu virus from the clade 2.3.4.4b has rapidly spread globally, causing disease in birds and non-human mammals; however, the prevalence in non-bird species remains low (AMSTAR rating 5/9; literature last searched 28 May 2024) • The zoonotic transmission risk of the circulating A(H5N1) clade 2.3.4.4b virus to the general population and beachgoers is currently low (AMSTAR rating 1/9; literature last searched 2023) • Scientists confirmed that the H5N1 clade 2.3.4.4 caused the deaths of five South polar skuas (a type of seabird) in Antarctica (Pre-print) • 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	• 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 workers and cullers, experienced relatively higher seroprevalence of A(H5N1) antibodies than non-poultry-exposed people; very low frequencies of

Circulating subtype or clade	Biology	Epidemiology	Diagnosis	Clinical presentation	Priority populations
	(prevalence rates ranging from 0.4% to 69.8%), there is an urgent need for standardized protocols and increased research in underrepresented regions to better understand influenza virus dynamics in water environments (AMSTAR rating 7/11; literature last searched 2023)	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 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)			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	• A low but present prevalence of influenza A virus (including 2.3.2.1c in Nigeria and 2.2.1.2 H5N1 and H5N2 viruses in Egypt) in African pigs was identified, along with potential transmission to other mammals, emphasizing the need for better surveillance in Africa (AMSTAR rating 7/11; literature last searched 2021) • From 2000 to 2022, 35 zoonotic diseases were identified in Cameroon, including H5N1 2.3.2.1c virus among the most reported, which emphasizes the need to better understand their distribution to develop prevention strategies (AMSTAR rating 7/11; literature last searched 2022)	• 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 jurisdictions organized by biology, epidemiology, diagnosis, clinical presentation, and priority populations

Organizing framework	Key findings

Biology	• In a joint assessment released on 23 April 2024 by the World Health Organization (WHO), Food and Agriculture Organization (FAO), and the World Organisation for Animal Health (WOAH), the entities indicated that 2.3.4.4b is diversifying genetically and spreading geographically, resulting in circulation in wild and migratory birds and poultry, wild carnivorous and scavenging mammals, domestic cats and dogs, and aquatic mammals.
	• A technical report updated on 26 April 2024 notes that the U.S. Centers for Disease Control and Prevention (CDC) is actively working on clade 2.3.4.4b viruses and is performing ongoing analyses of the virus to identify genetic changes, especially given that this genetic clade was found in dairy cattle in Texas.
	• To date, few genetic changes of public health concern have been identified in viruses circulating in wild birds and poultry.
	• The clade 2.3.2.1c of H5N1 was identified through genetic sequencing in two confirmed human cases in Cambodia.
	  ○ This clade was circulating in birds and poultry in Cambodia for several years.
	• In France, they found confirmed H5N1 among Muscovy ducks that had two-dose vaccinations.
	  ○ The second dose was given 41 days prior the infection.
	  ○ The European Food Safety Authority (EFSA) indicated that the humoral immune response and virological protection data suggest that vaccine protection was reduced post–second dose with increasing age of the ducks.

Epidemiology	*Overview*
	• According to Pan American Health Organization (PAHO), WHO, the European Centre for Disease Prevention and Control (ECDC), the EFSA, and the U.S. CDC, the overall risk to the public remains low.
	• According to the WHO Western Pacific region's weekly report on A(H5N1) and A(H5N6) (5 to 11 July 2024), the overall pandemic risk has not significantly changed in comparison to previous years.
	• The organizations recommended vigilance and ongoing surveillance of the global situation, particularly the migrating birds in the fall season.
	• The transmission of A(H5N1) is predominantly from wild birds, but there is evidence of other mechanisms of transmission (e.g., movement of cattle), which increases the likelihood of additional outbreaks in mammals and sporadic cases among humans.
	• The virus remains predominantly bound to avian-type receptors, which limits transmissibility to humans via respiratory droplets or fomites.
	• In an updated situation summary from the U.S. CDC from 16 May 2024, an ECDC weekly bulletin from 4 May 2024, and a joint assessment by the WHO, FAO, and WOAH released on 23 April 2024 reported that the overall risk for the public is low and those at risk of exposure is low-to-moderate.
	• The joint assessment and a WHO report from 28 March 2024 stated that there is currently no indication that the virus could cause an increased binding to receptors in the human upper respiratory tract, and therefore human-to-human transmission of the currently circulating virus is unlikely without further genetic changes.
	
	Humans
	• As of 30 June 2024, the Public Health Agency of Canada's (PHAC) recent Human Emerging Respiratory Pathogens Bulletin reported 11 human cases of A(H5N1) with one case in Australia, five in Cambodia, one in China, three in the United States, and one in Vietnam as of 30 June 2024.
	• Related to Australia's first human case of A(H5N1), it involved a two-and-a-half-year-old female child with no underlying conditions who travelled to Kolkata, India from 12 to 29 February 2024.
	  ○ The child's symptoms began on 25 February in India with loss of appetite, irritability, and fever, progressing to coughing and vomiting, leading to hospital admission in Australia on 2 March, intensive care unit transfer on 4 March.
	  ○ A nasopharyngeal swab and endotracheal aspirate taken on 6 and 7 March initially tested positive for influenza A and were later confirmed as A(H5N1) clade 2.3.2.1a by the WHO Collaborating Centre.

Organizing framework	Key findings
	○ The child is now reported to be clinically well. ○ The child had no known exposure to sick persons or animals during her stay, and close family contacts in Australia or India did not develop symptoms until 22 May 2024. ○ According to the WHO, the exposure of A(H5N1) clade 2.3.2.1a was likely in India, where this virus clade is known to circulate in birds. ○ The risk of sporadic human infections persists due to continued viral presence in poultry. • New developments have occurred since the release of the bulletin. ○ As of 9 July 2024, Cambodia reported two additional human cases of A(H5N1) infections, raising the total number of cases in Cambodia 2024 to seven. ○ The first new case was reported by Cambodia's ministry of health on 6 July 2024 and involved a three-year-old boy from the Takeo province who had symptoms of fever, coughing, and difficulty breathing and was hospitalized ○ Upon investigation, it was discovered that the boy had held a chicken 10 days earlier that had died in the village. ○ The second new case was reported on 8 July 2024 and involved the five-year-old cousin of the first new case who lived in the same home and had reportedly also made contact with the chicken that died. The girl had mild symptoms and is receiving treatment. ○ The clade of A(H5N1) in these new cases is unknown. ○ The Cambodian Ministry of Health highlighted most cases have been among children, half of whom ended up passing away. • In the U.S., there have been four confirmed human cases of A(H5N1) between 1 April 2024 to 3 July 2024. ○ The latest case was identified in the state of Colorado following an ongoing multistate outbreak of A(H5N1) in dairy cows. ○ The individual reported eye symptoms only and received oseltamivir treatment and has since recovered. • In May 2024, Mexico reported the first human case of A(H5N2), with the spectrum of the disease reported to be unknown. • One report from 4 July 2024 documented two cases of H5N6 avian influenza in Fujian Province, China, where both individuals had been exposed to poultry. ○ One case involved a 52-year-old female who developed symptoms on 13 April, was hospitalized on 22 April, and died on 30 April. ○ Another case involved a 41-year-old male who developed symptoms on 8 May, was hospitalized on 11 May, and died on the same day. • In Canada, there are no reported cases of transmission or sustained transmission of the disease to humans. *Birds* • Poultry continue to remain at risk from the continued circulation and spillover of H5N1 viruses from wild birds. • The ECDC weekly bulletin reported new recurrences of H5N1 in poultry and non-poultry birds. ○ The U.K. has self-declared zonal freedom from highly pathogenic avian influenza for Great Britain since 29 March 2024. ○ The U.K. does not currently have outbreaks of avian influenza in poultry or other captive birds and the current risk is low, however H5N1 continues to be found in wild birds in Great Britain and across Europe. ○ Since 1 February 2024, there have been eight cases of avian influenza found in wild birds across the U.K. and a mix of H5N1 and H5N5. • In France, a total of 25 avian influenza outbreaks were confirmed between 1 October 2023 and 14 June 2024, which include 10 virus detections of A(H5N1) in poultry, and 11 A(H5N1) and four A(H5Nx) in wild birds. ○ Over 650 European clade 2.3.4.4b A(H5) viruses have been characterized, 90% of which belong to six different A(H5N1) and one A(H5N5) genotypes. ○ One of these genotypes is EA-2022-BB (for the herring gull in France). • While no reports have been updated since January 2024, France confirmed H5N1 in a vaccinated Muscovy duck-housing establishment, affecting 8,700 ducks. ○ Additionally, another outbreak was detected in January 2024, causing the death of 40 ducks and presenting clinical signs of neurological disorders, and decreased food and water intake. • In Brazil, an outbreak of H5N1 in non-poultry birds was detected between 6 April 2024 to 3 May 2024. According to PAHO, there were seven outbreaks of avian influenza A(H5) in wild birds but no outbreaks in production birds or human cases between 1 January 2024 to 18 March 2024.

Organizing framework	Key findings

	• The Canadian Food Inspection Agency track estimates on the number of infected poultry flocks where H5N1 has been detected in Canada. They estimate that Alberta, British Columbia, Nova Scotia, Ontario, and Saskatchewan currently have infected premises.
	  ○ As of 10 July 2024, British Columbia has one active infected premise (confirmed by laboratory testing for the detection of H5N1, Saskatchewan has two infected premises, and 17 new positive and suspected cases of highly pathogenic avian influence (HPAI) A(H5Nx) across birds and mammals in Nova Scotia.
	Non-human mammals and animals
	• As of July 11 2024, the CFIA national avian influenza dashboard reported a total of 3 new positive A(H5Nx) and A(H5N1) cases appearing in red foxes, which were concentrated in coastal areas in Prince Edward Island.
	• According to the joint assessment by the WHO, FAO, and WOAH, spillover from birds to non-human mammals have been reported in the Americas and Europe, resulting in severe infection with neurological symptoms in some non-human mammals.
	• For example, the assessment reported that infected ferrets have led to severe disease.
	• The Canadian Food Inspection Agency in collaboration with Environment and Climate Change Canada and Canadian Wildlife Health Cooperative have a dashboard where they monitor H5Nx in different types of non-human mammals and animals.
	  ○ As of February 2024, there have been confirmed cases of either H5N1, H5, H5N5, or a combination across all the provinces.
	Cattle
	• The PAHO public health risk assessment of the spread of avian influenza A(H5N1) clade 2.3.4.4b on 12 July 2024, indicated there are localized occurrences of A(H5N1) clade 2.3.4.4b in dairy cattle herds in the U.S., with spillover into humans and other mammals who were in direct contact.
	• As of 5 July 2024, 12 states in the U.S. have now confirmed H5N1 clade 2.3.4.4b among 139 dairy cow herds.
	• A technical report updated on 5 June 2024 (the July update has not yet been released) notes that the CDC continues to actively work on clade 2.3.4.4b viruses and is performing ongoing analyses of the virus to identify genetic changes.
	• On 6 June 2024, a PHAC assessment on the risk scenario of influenza A(H5Nx) clade 2.3.4.4b virus and related viruses found that cattle-to-cattle transmission of influenza A(H5Nx) clade 2.3.4.4b virus is occurring, but transmission is complex, and concerns remain about the virus's ability to reassort.
	• The joint assessment by the WHO, FAO, and WOAH reported H5N1 detection in dairy cattle in the U.S and in neonatal goats who share the same space as poultry.
	• The U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service provides regular updates on detections in dairy cattle and updated epidemiological reports and guidance for farmers and veterinarians.
	• The U.S. Food & Drug Administration (FDA) completed 297 retail dairy samples, and all were found negative as of 10 May 2024.
	  ○ As of 10 May 2024, all egg inoculation tests related to retail sampling have been completed and were found negative; continued surveillance and sampling will continue.
	• The ECDC weekly bulletin reported no cases in cattle in Europe.
	• According to PHAC, as of 16 May 2024, highly pathogenic avian influenza has not been detected in cattle or livestock (apart from poultry) in Canada, and the risk of transmission to humans remains low.
	  ○ The Canadian Food Inspection Agency in collaboration with Health Canada and PHAC have been proactively testing commercial milk samples across Canada to detect fragments of the virus.
	  ○ As of 14 May 2024, all tested samples have been negative.

Diagnosis	• There is updated guidance on testing, reporting and lab information on the use of RT-PCR assay using H5-specific primers and probes from the U.S. CDC. • The USDA released recommendations on 14 May 2024 related to H5N1 virus in livestock for state animal health officials, veterinarians, and producers. • The WOAH indicated that H5Nx in non-avian species (including cattle and other livestock populations) should have a differential diagnosis especially among animals that are showing clinical symptoms, sick or dead domestic animals near affected areas, and suspected animals that may be exposed or linked to suspected or confirmed H5Nx in birds or cattle.

Organizing framework	Key findings
	• In Australia, diagnostic efforts involve PCR and ELISA methods, with avian influenza being a nationally notifiable disease. • The French Agency for Food, Environmental and Occupational Health and Safety (ANSES) is committed to combating the spread against the disease by coordinating the diagnosis of avian influenza in animals and conducting research to improve virus detection. • The BC Centre for Disease Control use nucleic acid testing and Public Health Ontario use RT-PCR to detect the presence of H5N1.

Clinical presentation	• In humans, symptoms and conditions ranged from asymptomatic to severe illness in humans such as fever, fatigue, cough, abdominal pain, diarrhea, pneumonia, sepsis and acute respiratory distress syndrome.
	  ○ Some countries such as Vietnam and China reported deaths due to complications.
	  ○ In the case of the exposure from dairy cattle in the U.S., the patient reported eye redness (consistent with conjunctivitis) as their only symptom.
	• In birds, clinical symptoms include a lack of energy or food intake, decreased egg production, shell-less or soft-shelled eggs, swelling in extremities, respiratory and neurological issues, diarrhea, and sudden death.
	  ○ In the January 2024 outbreak in France, ducks presented neurological disorders, decreased food and water intake, and reported death.
	• According to the USDA, dairy cattle may experience sudden drop food intake, marked or acute drop in milk production, thickened milk or no milk, and respiratory signs such as clear nasal discharge.

Priority populations	• We found limited publicly available information about priority populations. • Confirmed human cases were those in close contact with or handling cattle and birds (e.g., poultry markets and backyard poultry, wild birds).

Appendix 4: Key findings from evidence syntheses organized 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
  ○ Circulating clades
    ▪ 2.3.4.4b
• Epidemiology (including transmission)
  ○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)
• Clinical presentation
  ○ Signs and symptoms
  ○ Risk factors
  ○ Disease/illness course
	The H5N1 avian flu virus from the clade 2.3.4.4b has rapidly spread globally, causing disease in birds and non-human mammals
	• The rapid spread of the disease is likely attributed to the global circulation of the H5N1 strain through migration patterns of birds.
	• Prevalence of the disease in animal populations, besides from birds, is low but highly pathogenic.
	• Mortality and disease symptoms vary between species.
	• Mammals typically experience flu-like symptoms, including fever and runny nose, as well as respiratory distress, and neurological impairments.
		High	No	5/9	28 May 2024	No	None identified

• Biology
  ○ Circulating clades
    ▪ 2.3.4.4b
  ○ Genomic changes and impacts
    ▪ Infectivity/transmission
• Epidemiology (including transmission)
  ○ Route of transmission
    ▪ Bird/non-human mammal to human (i.e., zoonotic transmission)
	The zoonotic transmission risk of the circulating A(H5N1) clade 2.3.4.4b virus to the general population and beachgoers is currently low
	• This review examined the existing literature to assess avian influenza virus transmission risks to beachgoers and the general population.
	• Current epidemiological and virological evidence suggests that the H5N1 virus has not yet developed the ability to transmit between humans, resulting in low risks from zoonotic transmission and waterborne infection.
	• Different clades of H5N1 may lack the mechanism to attach to human receptors and replicate in human cells.
	• H5N1 virus can survive in aquatic environments, such as beaches, aquatic sediments, and surface water, particularly under cold temperatures, low salinity, and neutral pH.
	• While the fecal-oral route is the primary transmission method for avian influenza A(H5N1) among birds, there is currently no evidence of direct transmission to humans via ingestion of contaminated water.
		High	N/A	1/9	2023	N/A	None identified

• Epidemiology (including transmission) ○ Route of transmission	The ongoing H5N1 panzootic event has significantly impacted biodiversity and mammalian	High	No	4/9	2023	No	Occupation

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
▪ Bird to non-human mammal ▪ Non-human mammal to mammal (including development of a non-human mammal reservoir) ▪ Bird/non-human mammal to human (i.e., zoonotic transmission) o Immunological characteristics ▪ Innate ▪ Adaptive ▪ Antigen/antibody and cellular immune responses (including cross-protection and cross-reactivity with other human influenza viruses, seasonal strains) • Diagnosis o Molecular methods for rapid detection o Serological diagnostics (e.g., self-testing, point-of-care diagnostics) • Priority populations o Groups at higher risk of exposure ▪ Working on a commercial poultry farm (e.g., producer, seasonal/migrant workers)	health due to multiple factors (e.g., broader geographic impact, increased number of infected mammal species, potential for mammal-to-mammal transmission), highlighting the importance of continuous surveillance and international collaboration						
• Biology o Circulating clades ▪ 2.3.4.4b o Genomic changes and impacts ▪ Infectivity/transmission ▪ Pathogenicity ▪ Virulence/disease severity ▪ Mammalian adaptation ▪ Antiviral susceptibility o Virological characteristics ▪ Infectivity/transmission ▪ Pathogenicity ▪ Virulence/disease severity • Epidemiology (including transmission) o Route of transmission	Given the significant presence of influenza A viruses in various water matrices associated with poultry (prevalence rates ranging from 4.3% to 76.4%) and wild bird habitats (prevalence rates ranging from 0.4% to 69.8%), there is an urgent need for standardized protocols and increased research in underrepresented regions to better understand influenza virus dynamics in water environments • The findings also highlighted that influenza B detection was limited across water environments and, of the identified studies, there was a lack of research on influenza in pig-associated water environments.	High	No	7/11	2023	No	None identified

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
▪ Bird to non-human mammal ▪ Non-human mammal to mammal (including development of a non-human mammal reservoir) • Bird/non-human mammal to human (i.e., zoonotic transmission)							
• Epidemiology (including transmission) o Route of transmission ▪ Bird/non-human mammal to human (i.e., zoonotic transmission) o Reported cases and other epidemiological indicators of avian influence • Priority populations o Groups at higher risk exposure ▪ Working on a commercial poultry farm (e.g., producer, seasonal/migrant workers) ▪ Working with non-commercial or backyard flocks ▪ Working with live or recently killed poultry, cattle, or other livestock (e.g., butcher, processing plant worker, poultry culler) ▪ Meat/milk processes plan worker	All reported cases of H5N6 in humans had prior contact with birds and were found to have a high disease severity, with 95% of cases resulting in hospitalization • The literature review identified 85 reported cases of AH5N6 and synthesized the case reports. • The median ages of those infected was 50 years old, with 13 cases reported in children. • In all cases, there was known contact with birds prior to the onset of illness, with contact methods including visiting live bird markets, employment as a poultry worker or exposure to slain and cooked poultry or domestic and backyard poultry. • Almost all cases have been reported from China, from 15 different provinces, with the exception of one case in Laos. • Disease severity is quite high, with 95% of those infected requiring hospital admission within one week of illness onset. • Symptoms often begin with a fever, upper respiratory tract symptoms and myalgia followed by rapid progression to the lower respiratory tract, multiple organ failure, and acute respiratory distress syndrome. • Outcome data was only available for half the cases and of these individuals two-thirds died.	High	No	1/9	2021	No	None reported
• Biology o Virological characteristics ▪ Infectivity/transmission	The evolution and host adaptation of influenza A virus (IAV) in bovine species has been hindered until the emergence of novel influenza D virus in cattle, as some bovine host factors that may have anti-influenza properties could have provided IAV resilience for bovines, but more research is needed to ascertain host-specific factors that have	Medium	No	1/9	2019	No	No

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
	contributed to this differential pathogenic response and disease progression in bovines • The distribution of influenza A over the last 45 years show that it has evolved in "almost all mammalian hosts at the human–animal interface, except in bovine species." • There have been natural cases of influenza in bovines that cause influenza-like respiratory disease (e.g., with bronchopneumonia, epizootic cough, nasal discharge, lacrimation, other extrapulmonary signs such as milk drop), but only very few have resulted in virus isolation. • IAV strains with cattle origin were first isolated in the early 1970s at the same time when human IAV strains were prevalent (H3N2) but there is limited evidence for genetic relatedness.						
• Biology ○ Circulating clades ▪ 2.3.2.1c ▪ Other (if new subtypes identified as having emerged) ○ Genomic changes and impacts ▪ Infectivity/transmission ▪ Mammalian adaptation • Epidemiology (including transmission) ○ Route of transmission ▪ Bird to non-human mammal ▪ Non-human mammal to mammal (including development of a non-human mammal reservoir, bovines, and other livestock) • Priority populations ○ Groups at higher risk of exposure ▪ Livestock farm worker/small herd owner ▪ Meat/milk processing plant worker	A low but present prevalence of influenza A virus (including 2.3.2.1c in Nigeria, 2.2.1.2 H5N1 and H5N2 viruses in Egypt) in African pigs was identified, along with potential transmission to other mammals, emphasizing the need for better surveillance in Africa	Medium	No	7/11	2021	No	Occupation
• Biology ○ Circulating clades ▪ 2.3.2.1c ○ Genomic changes and impacts	From 2000 to 2022, 35 zoonotic diseases were identified in Cameroon, including H5N1 2.3.2.1c virus among the most reported, which emphasizes	Low	No	7/11	2022	No	Occupation

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
▪ Mammalian adaptation o Virological characteristics ▪ Infectivity/transmission • Priority populations o Groups at higher risk of exposure ▪ Working on a commercial poultry farm (e.g., producer, seasonal/migrant workers)	the need to better understand their distribution to develop prevention strategies						
• Biology o Virological characteristics ▪ Infectivity/transmission • Epidemiology o Route of transmission ▪ Environmental viral load (e.g., avian and mammalian viral shedding) o Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution) • 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 ▪ Infectivity/transmission • Epidemiology (including transmission) o Route of transmission	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.	High	No	2/9	31 July 2022	No	No

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
▪ Bird/non-human mammal to human (i.e., zoonotic transmission) ○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)	• Infections were almost exclusively associated with human contact with infected birds.						
• Biology ○ Circulating clades ▪ 2.3.4.4b ○ Virological characteristics ▪ Virulence/disease severity ○ Immunological characteristics ▪ Antigen/antibody and cellular immune responses (including cross-protection and cross-reactivity with other human influenza viruses, seasonal strains) • Epidemiology (including transmission) ○ 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 ○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution) • Diagnosis ○ Serological diagnostics (e.g., self-testing, point-of-care diagnostics) • Priority populations ○ Groups at higher risk of exposure ▪ Working on a commercial poultry farm (e.g., producer, seasonal/migrant workers)	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

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
▪ Breeding and handling birds (e.g., dealer, breeder of exotics, falconry, racing pigeons) ▪ Working with live or recently killed poultry, cattle, or other livestock (e.g., butcher, processing plant worker, poultry culler) ▪ Working with wild birds and/or mammals for healthcare, research, and conservation (e.g., laboratory workers, researchers, biologists, wildlife rehabilitators, persons permitted to perform bird branding, capturing, sampling, removal, restoration) ▪ Working or visiting live bird or mammal markets ▪ Working in healthcare settings and other contacts of cases (if human-to-human transmission starts)							
• Epidemiology (including transmission) o Route of transmission ▪ Bird to non-human mammal o 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	No	4/9	2019	No	None identified

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

	• 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.						

• Epidemiology (including transmission)
  ○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)
• Diagnosis
  ○ 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
		High	No	3/9	10 June 2019	No	None identified

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
	lack of standardized protocols and methods in the literature.						

• 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) (e.g., prevalence, case fatality rates, geographic distribution)
• Diagnosis
  o Molecular methods for rapid detection
  o Serological diagnostics (e.g., self-testing, point-of-care diagnostics)
	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) 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.
		High	No	7/11	20 October 2018	No	None identified

• Epidemiology (including transmission)
  o 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
		High	No	6/11	20 September 2018	No	None identified

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
	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 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%.						
• Epidemiology (including transmission) o Route of transmission ▪ Bird/non-human mammal to human (i.e., zoonotic transmission) ▪ Human to human o 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. o Most cases were reported in Egypt, followed by Indonesia, Vietnam, Cambodia, and mainland China. o A seasonal peak in the winter was detected among these countries. o Most of the cases were found among children and younger adults, with a higher proportion of women in Southeast Asia and China. o 97.4% were linked to poultry exposure, suggesting limited human-to-human transmission. • Other subtypes like H5N6 were linked with causing deaths.	High	No	2/9	31 July 2019	No	None identified

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
	• 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) o 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 o Route of transmission ▪ Bird to non-human mammal o Reported cases and other epidemiological indictors of avian influenza o Susceptibility and transmission parameters ▪ Latent period ▪ Infectious period	Contextualizing species and virus type is important in understanding parameters of 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 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. o 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. • 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.	High	No	5/10	2021	Not available	None identified
• Epidemiology o Route of transmission ▪ Bird to non-human mammal • Priority populations	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	High	No	5/9	2019	Not available	• Occupation

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
○ Groups at higher risk of exposure ▪ Working on a commercial poultry farm (e.g., producer, seasonal/migrant workers)	• 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 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.						
• Biology ○ Virological characteristics ▪ Infectivity/transmission ▪ Pathogenicity • Epidemiology ○ Route of transmission ▪ Environmental viral load (e.g., avian and mammalian viral shedding) ○ Susceptibility and transmission parameters ▪ Virus shedding	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 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.	High	No	4/11	2017	Not available	None identified

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

	• 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:
	  o respiratory shedding was higher than cloacal shedding
	  o higher shedding through the respiratory tract was observed in ducks than in chickens
	  o lower shedding through the cloaca was observed in ducks than in chickens.
	• For low pathogenicity avian influenza viruses:
	  o similar shedding through the respiratory and digestive tracts was seen in ducks and chickens
	  o higher shedding through the cloaca was observed in ducks than in chickens
	  o 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
  o Route of transmission
    ▪ Bird to non-human mammal
  o Reported cases and other epidemiological indictors of avian influenza
• Diagnosis
  o Serological diagnostics (e.g., self-testing, point-of-care diagnostics)
	<u>Surveillance and serosurveillance of the avian influenza in wild birds is important to monitor its risk of transmission to other species</u>
	• 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%,
		Medium	No	6/11	2021	Not available	None identified

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
	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 (e.g., avian and mammalian viral shedding) • 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 5: Key findings from single studies organized by relevance

<table>
<tr><th>Dimension of organizing framework</th><th>Declarative title and key findings</th><th>Relevance rating</th><th>Study characteristics</th><th>Equity considerations</th></tr>
<tr><td>Epidemiology (including transmission)
Route of transmission
Environmental viral load (e.g., avian and mammalian viral shedding)
Clinical presentation
Signs and symptoms
Priority human populations
Groups at higher risk of exposure
Working with unpasteurized milk products (e.g., milk processing plant worker, cheesemaker)</td><td>Dairy cattle are susceptible to infection with highly pathogenic avian influenza (HPAI) H5N1 virus and can shed virus in milk and, therefore, might potentially transmit infection to other mammals via unpasteurized milk
Milk samples and fresh and formalin-fixed tissues from dairy cattle were received from Texas on 21 March and from Kansas on 22 March 2024.
A reduction in milk production and vague systemic illness were the most reported clinical signs in affected cows, but neurologic signs and death rapidly developed in affected domestic cats.
Ingestion of feed contaminated with feces from wild birds infected with the HPAI virus is believed to be the most likely initial source of infection in dairy farms; migratory birds (Anseriformes and Charadriiformes) are considered likely culprits because the Texas Panhandle region is situated in the Central Flyway, where these birds are the primary natural reservoir for avian influenza viruses.</td><td>High</td><td>Focus of the study:
Evaluating the transmission of influenza A virus in cow dairy farms in Kanas and Texas

Publication date:
July 2024

Jurisdiction studied:
U.S.

Methods used:
Geospatial analysis</td><td>None reported</td></tr>
<tr><td>Epidemiology (including transmission)
Route of transmission
Bird/non-human mammal to human (i.e., zoonotic transmission)</td><td>An outbreak among Texas dairy cattle revealed the emergence of an avian influenza A(H5N1) with significant novel mutations, identified potential spillover to humans causing mild to moderate influenza-like symptoms, and highlighted the necessity for further studies on the virus's pathogenicity and transmission dynamics
The study highlighted that H5N1 was solely detected in sick cows (mainly in nasal swabs), indicating respiratory transmission among cattle, and found high genetic similarity between the H5N1 strain in cattle and strains in birds and humans (i.e., it suggests a single interconnected multispecies outbreak in Texas).</td><td>High</td><td>Focus of the study:
Investigating the outbreak of illness among Texas dairy cattle, particularly the detection and analysis of highly pathogenic avian influenza A(H5N1)

Publication date:
July 2024

Jurisdiction studied:
U.S.
Methods used:
Descriptive study using molecular screening, cell culture, metagenomics, and next-generation sequencing</td><td>None reported</td></tr>
<tr><td>Epidemiology (including transmission)
Route of transmission
Bird/non-human mammal to human (i.e., zoonotic transmission)</td><td>Holstein dairy cows naturally infected with A(H5N1) virus showed significant viral presence in their mammary glands and milk, highlighting the virus's adaptability and potential cross-species transmission</td><td>Medium</td><td>Focus of the study: Focuses on the presence and pathogenesis of A(H5N1) virus in the respiratory and mammary tissues of naturally infected Holstein dairy cows</td><td>None reported</td></tr>
</table>

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
			Publication date: July 2024 *Jurisdiction studied:* U.S. *Methods used:* Descriptive observational study	

• Biology
  ○ Circulating clades
    ▪ 2.3.4.4b
  ○ Genomic changes and impacts
    ▪ Pathogenicity
  ○ Virological characteristics
    ▪ Pathogenicity
• Epidemiology (including transmission)
  ○ Route of transmission
    ▪ Bird to non-human mammal
    ▪ Non-human mammal to mammal (including development of a non-human mammal reservoir, bovines and other livestock)
	An experimental study discovered that European highly pathogenic avian influenza (HPAI) A(H5N1) has the ability to cause infection and proliferate in bovine epithelial cells, similar to the North American lineage HPAI A(H5N1)	High	*Focus of the study:*
			Determining how susceptible bovine epithelial cells are to the European lineage H5N1 infection
			
			Publication date:
			26 June 2024
			
			Jurisdiction studied:
			U.S.
			
			Methods used:
			Experimental
				• None reported

• Biology
  ○ Circulating clades
    ▪ 2.3.4.4b
• Epidemiology (including transmission)
  ○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)
	Early monitoring for the presence of H5 RNA in milk from dairy cattle is important to prevent outbreaks of the virus and transmission of the virus to humans (Pre-print)
	• As of June 2024, all samples of milk tested in Canada were H5 RNA negative.
		High	*Focus of the study:*
			To monitor the prevalence of H5 RNA in dairy cattle milk in Canada
			
			Publication date:
			26 June 2024
			
			Jurisdiction studied:
			Canada
			
			Methods used:
			Surveillance
				• None reported

• Biology
  ○ Circulating clades
    ▪ 2.3.4.4b
• Epidemiology (including transmission)
  ○ Route of transmission
    ▪ Bird to non-human mammal
	A surveillance study in New York showed that birds containing the A(H5N1) virus are present in urban areas; therefore, urban based surveillance programs are essential to monitor the spread of the A(H5N1) virus at the animal-human interface
	• High density urban areas have a higher chance of infection from direct contact with infected birds and indirect contact through contaminated water sources and bird faeces.
		Medium	*Focus of the study:*
			To monitor the prevalence of H5N1 in an urban environment
			
			Publication date:
			15 May 2024
				• None reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
▪ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)	• The A(H5N1) virus can spread to pets, including cats and dogs, further increasing the risk of animal-to-human transmission in urban areas.		*Jurisdiction studied:* U.S. *Methods used:* Surveillance	
• Epidemiology (including transmission) o Route of transmission ▪ Bird to non-human mammal	A geospatial and exposure analysis found that non-waterfowl species had the highest dairy farm exposure, with other factors (i.e., livestock trade, poultry litter feed, contaminated milking machinery) also contributed to the amplification of the outbreaks in the United States (Pre-print)	High	*Focus of the study:* Evaluating the introduction and transmission of dairy farms in the U.S. *Publication date:* 4 May 2024 *Jurisdiction studied:* U.S. *Methods used:* Geospatial analysis	• None reported
• Biology o Genomic changes and impacts ▪ Infectivity/transmission ▪ Pathogenicity ▪ Virulence/disease severity o Immunological characteristics ▪ Innate ▪ Adaptive ▪ Antigen/antibody and cellular immune responses (including cross-protection and cross-reactivity with other human influenza viruses, seasonal strains)	Influenza A virus receptors found in humans, ducks, and chicken were widely expressed in the bovine mammary gland and respiratory tract, which the authors suggest helps to explain the high levels of H5N1 virus in infected bovine milk and the potential to lead to novel genomic changes in influenza A virus (Pre-print)	Medium	*Focus of the study:* Understanding the cell receptors in bovine tracheal and lung tissues *Publication date:* 3 May 2024 *Jurisdiction studied:* U.S. *Methods used:* Immunology study	• None reported
• Biology o Circulating clades ▪ 2.3.4.4b o Genomic changes and impacts ▪ Infectivity/transmission ▪ Pathogenicity ▪ Virulence/disease severity ▪ Mammalian adaptation ▪ Antiviral susceptibility o Virological characteristics	The circulation of clade 2.3.4.4b B3.13 virus among dairy cattle poses a potential zoonotic threat, requiring continued monitoring to inform epidemiological risk and early warning for any interspecies transmission (Pre-print) • The authors concluded that infected cows may shed virus for two to three weeks. • The study found amino acid mutations associated with mammalian adaptation, indicating an approximately four months of evolution with limited local circulation in dairy cattle.		*Focus of the study:* Determining how transmission in dairy cattle affects genomic diversity and whether changes could lead to dairy cattle to be host reservoir for influenza A virus and zoonotic potential *Publication date:* 1 May 2024	• None reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
▪ Infectivity/transmission ▪ Pathogenicity ▪ Virulence/disease severity • Epidemiology (including transmission) o Route of transmission	• Low-frequency sequence variants were detected, which poses the threat of increased probability of phenotypes that may increase interspecies transmission.		*Jurisdiction studied:* U.S. *Methods used:* Phylodynamic analysis	
• Biology o Circulating clades ▪ 2.3.4.4b • Epidemiology (including transmission) o Route of transmission • Diagnosis o Molecular methods for rapid detection o Serological diagnostics (e.g., self-testing, point-of-care diagnostics)	Scientists confirmed that the H5N1 clade 2.3.4.4 caused the deaths of five South polar skuas (a type of seabird) in Antarctica (Pre-print) • Samples were collected from James Ross Island and results were confirmed by specific real-time RT-PCR reactions.		*Focus of the study:* Identifying confirmed cases of H5N1 among birds *Publication date:* 11 April 2024 *Jurisdiction studied:* Antarctica *Methods used:* Surveillance study	• None reported
• Biology o Virological characteristics ▪ Infectivity/transmission ▪ Pathogenicity ▪ Virulence/disease severity o Immunological characteristics ▪ Innate ▪ Adaptive ▪ Antigen/antibody and cellular immune responses (including cross-protection and cross-reactivity with other human influenza viruses, seasonal strains)	H5N1 influenza A virus replicated with high efficacy in precision-cut lung slices from human donors of different ages, with reduced replication among older donors compared to younger donors (Pre-print) • Influenza A infection caused significant cytotoxicity and significant early interferon responses. • The precision-cut lung slices responded by IL-6 and IP-10/CXC10 mrNAs.	Medium	*Focus of the study:* Evaluating lung aging on the efficiency of influenza A virus replication and antiviral response *Publication date:* 16 April 2024 *Jurisdiction studied:* U.S. *Methods used:* Immunology study	• None reported
• Biology o Circulating clades ▪ 2.3.4.4b ▪ 2.3.2.1c o Genomic changes and impacts ▪ Infectivity/transmission ▪ Pathogenicity ▪ Virulence/disease severity o Virological characteristics ▪ Infectivity/transmission ▪ Pathogenicity	Between December 2023 and March 2024, Europe saw fewer but still widespread outbreaks of highly pathogenic avian influenza A(H5) in domestic and wild birds, with most outbreaks originating from wild birds, while outside Europe, North America remained a hotspot with goat kids in the U.S. found infected with avian influenza A(H5N1) virus representing the first natural infection in any ruminant species worldwide • Human infections remained rare during this time, with no evidence of sustained human-to-human transmission. • The risk of infection for the general population in Europe is low, but higher for those exposed to infected animals.	High	*Focus of the study:* To provide an overview of avian influenza worldwide between December 2023 and March 2024 *Publication date:* 2024 *Jurisdiction studied:* Global *Methods used:* Surveillance data	• Occupation

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
▪ Virulence/disease severity o Immunological characteristics ▪ Innate ▪ Adaptive ▪ Antigen/antibody and cellular immune responses (including cross-protection and cross-reactivity with other human influenza viruses, seasonal strains) • Epidemiology (including transmission) o Route of transmission ▪ Bird to non-human mammal ▪ Non-human mammal to mammal (including development of a non-human mammal reservoir) ▪ Bird/non-human mammal to human (i.e., zoonotic transmission) o Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution) • Priority populations o Groups at higher risk of exposure ▪ Working on a commercial poultry farm (e.g., producer, seasonal/migrant workers) ▪ Working with non-commercial or backyard flocks ▪ Breeding and handling birds (e.g., dealer, breeder of exotics, falconry, racing pigeons) ▪ Livestock farm worker/small herd owner				
• Epidemiology o Route of transmission ▪ Non-human mammal-to-mammal (including development of a non-human mammal reservoir, bovines, and other livestock)	Cow-to-cow transmission of H5N1 was reported in dairy cattle in the U.S., with cows experiencing apparent systemic illness, an abrupt drop in milk production, reduced feed intake and rumination, abundant virus shedding, and the production of thick, creamy yellow milk	High	*Focus of the study:* To describe the cases of H5N1 among dairy cattle *Publication date:* March 2024 *Jurisdiction:* U.S.	• None reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
○ Susceptibility and transmission parameters ▪ Clinical illness period ○ Clinical presentation	• The most likely initial source of infection in the dairy farms is presumed to be ingestion of feed contaminated with feces from wild birds, but the exact source of the virus is unknown. • Migratory birds (Anseriformes and Charadriiformes) are likely sources in the Texas panhandle. • On affected farms incidence peaked four to six days after animals were first affected and then tapered off between 10 and 14 days. • Minimal cattle death was reported, though deaths of wild birds and domestic cats were observed in affected sites. • The route of exposure among domestic cats were likely from the consumption of unpasteurized milk and colostrum, leading to rapid onset of neurologic signs, blindness, and death. • H5N1 can shed virus in milk, which might potentially lead to transmission to other mammals via unpasteurized milk. • Continued surveillance of highly pathogenic avian influenza viruses among domestic production animals is required to understand the virus evolution, pathogenesis, and prevent cross-species and mammal-to-mammal transmission. • The findings suggest cross-species and mammal-to-mammal transmission of H5N1.		*Methods:* Case description	
• Epidemiology ○ Route of transmission	Wild waterfowl travel up to 1251 km to visit commercial livestock facilities and act as a potential transmission pathway for avian influenza to livestock; as a result small or isolated natural and artificial water or food sources in or near livestock facilities increase the likelihood of attracting these birds	Medium	*Focus of the study:* To document the movement patterns of wild waterfowl *Publication date:* January 2022 *Jurisdiction:* U.S. *Methods:* Telemetry and GPS tracking	• None reported

Appendix 6: Detailed jurisdictional scan about what is known about the emergence, transmission and spectrum of the burden of disease of avian influenza A(H5Nx) subtypes in countries and international organizations

Jurisdiction	Dimension of the organizing framework	Key findings
Pan-Organizations	• Biology ○ Circulating clades ▪ 2.3.4.4b ○ Virological characteristics ▪ Infectivity/transmission ▪ Pathogenicity ▪ Virulence/disease severity • Epidemiology (including transmission) ○ Route of transmission ▪ Bird to non-human mammal ▪ Bird/non-human mammal to human (i.e., zoonotic transmission) ▪ Environmental viral load (e.g., avian and mammalian viral shedding) ○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)	• The Pan American Health Organization (PAHO) released a public health risk assessment of the spread of avian influenza A(H5N1) clade 2.3.4.4b on 12 July 2024, indicating that the overall risk to the public is low based on the available information (level of confidence is moderate). ○ The epidemiological data indicate localized occurrences of A(H5N1) clade 2.3.4.4b in dairy cattle herds in the U.S., with spillover into humans and other mammals who were in direct contact. ○ The virus remains predominantly bound to avian-type receptors, which limits transmissibility to humans via respiratory droplets or fomites. ○ Transmission is predominantly from wild birds but there is evidence of other mechanisms of transmission (e.g., movement of cattle), which increases the likelihood of additional outbreaks in mammals and sporadic cases among humans. ○ PAHO and the World Health Organization (WHO) both consider the risk to be low, but emphasize the need for vigilance and ongoing monitoring of the situation. • In the weekly bulletin Communicable Disease Threats Report posted on 12 July 2024, the European Centre for Disease Prevention and Control (ECDC) indicated that the overall public health risk to be low and low-to-moderate risk for those in close contact with infected animals or contaminated environments. ○ In two reports from 8 July 2024 and 20 June 2024, the ECDC indicated that there have been no confirmed cases of A(H5N1) in Europe; however, increased vigilance is recommended. • The WHO Western Pacific Region release weekly reports on A(H5N1) and A(H5N6) and reported no new human infections between 5 to 11 July 2024. ○ During the week of 5 to 11 July 2024, there have been no new cases of human inflection for A(H5N1) and A(H5N6). ○ The last A(H5N6) case reported was from China on 8 May 2024. ○ The overall pandemic risk has not significantly changed in comparison to previous years. • A report from the European Food Safety Authority from 4 July 2024 indicated that the number of outbreaks of avian influenza in birds has decreased in Europe, but it is important to increase the surveillance to face the new season when migrating birds arrive in the fall. The risk for the general population is reported to be low. • The World Organisation for Animal Health (WOAH) released two situation reports since 3 May 2024, with the latest covering 5 to 21 June 2024. ○ The number of new outbreaks and events in birds is relatively low, which is consistent with the seasonality of highly pathogenic avian influenza (HPAI) in poultry. ○ During the three-week period, there were 166,000 poultry birds that died or were culled. ○ There are ongoing events of A(H5N1) among poultry and dairy cattle in the U.S, in France, China and Poland for non-poultry birds. • The latest WHO Influenza at the Human-Animal Interface report summarized findings between 4 May to 7 June 2024. ○ Between this period, there were four human cases of A(H5N1), one human case of A(H5N2), and two human cases of A(H5N6). • PAHO released an epidemiological update of A(H5N1) on 5 June 2024.

Jurisdiction	Dimension of the organizing framework	Key findings
		○ The document provides updates on number of outbreaks in birds and mammals between 2022 to 2024 in addition to the type of mammals. • The WHO, Food and Agriculture Organization (FAO), and World Organisation for Animal Health (WOAH) released a joint assessment of the resent influenza A(H5N1) viruses on 23 April 2024. ○ Based on current available information, the WHO assess the overall public health risk as low, and for those at risk of exposure that risk is low to moderate. ○ The role of consumption and handling milk and milk products and the role of pasteurization is currently being investigated. ○ There is currently no indication that the virus could cause an increased binding to receptors in the human upper respiratory tract, therefore human-to-human transmission of the currently circulating virus is unlikely without further genetic changes. ○ Clade 2.3.4.4b is diversifying genetically and spreading geographically, resulting in circulation in wild and migratory birds and poultry, wild carnivorous and scavenging mammals, domestic cats and dogs, and aquatic mammals. ○ Spillover from birds to mammals have been reported in the Americas and Europe, resulting in severe infection with neurological symptoms in some mammals. ○ The assessment reported H5N1 detection in neonatal goats who share the same space as poultry and in dairy cattle in the U.S. ○ Lateral transmission among cattle likely occurred in the U.S., while the frequency of cattle-to-bird transmission is unknown. ○ Poultry continues to remain at risk from the continued circulation and spillover of H5N1 viruses from wild birds. ○ As of 20 April 2024, no markers of mammalian adaptation have been found in dairy cattle. ○ Viruses in infected ferrets have led to severe disease. ○ The human case in the U.S. had markers associated with mammalian adaptation in the PB2 gene segment. • There have been two updates to the WHO Influenza at the Human-Animal Interface since 1 February 2024, one reported for 22 December 2023 to 26 February 2024 and the other from 27 February to 28 March 2024. • The ECDC released an avian influenza overview report from December 2023–March 2024 that highlights virus detections and human cases in Europe and outside of Europe.
Australia	• Biology ○ Circulating clades ▪ 2.3.4.4b ○ Virological characteristics ▪ Infectivity/transmission ▪ Pathogenicity ▪ Virulence/disease severity • Epidemiology (including transmission) ○ Route of transmission ▪ Bird to non-human mammal ▪ Bird/non-human mammal to human (i.e., zoonotic transmission) ▪ Environmental viral load (e.g., avian and mammalian viral shedding)	• According to the Australian Centre for Disease Control, Australia has one reported case of bird flu in a human in 2024, as of 17 June 2024. ○ This case was contracted overseas, and there's no evidence of easy human-to-human transmission of bird flu strains found globally. • The WHO Collaborating Centre (WHOCC) in Australia was notified of a suspected human avian influenza A(H5N1) case on 17 May 2024, which was confirmed on 18 May, notified to WHO on 22 May; this was reported by WHO on 7 June 2024. ○ The case involved a two-and-a-half-year-old female child with no underlying conditions who travelled to Kolkata, India from 12 to 29 February 2024, had no known exposure to sick persons or animals during her stay, and whose close family contacts in Australia or India did not develop symptoms until 22 May 2024. ○ The child's symptoms began on 25 February in India with loss of appetite, irritability, and fever, progressing to coughing and vomiting, leading to hospital admission in Australia on 2 March, intensive care unit transfer on 4 March, and discharge after 2.5 weeks, with the child now reported to be clinically well.

Jurisdiction	Dimension of the organizing framework	Key findings
	○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)	○ A nasopharyngeal swab and endotracheal aspirate taken on 6 and 7 March initially tested positive for influenza A and were later confirmed as A(H5N1) clade 2.3.2.1a by the WHOCC. ○ India reported avian influenza A(H5N1) in domestic birds in 2024, and while this is Australia's first human case, it was likely contracted in India where this virus clade is known to circulate in birds; the risk of sporadic human infections persists due to continued viral presence in poultry.
Brazil	• Biology ○ Virological characteristics ▪ Infectivity/transmission • Epidemiology (including transmission) ○ Route of transmission ▪ Environmental viral load (e.g., avian and mammalian viral shedding) • Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)	• No new relevant experiences found between 14 May to 8 July 2024. • An ongoing outbreak of A(H5N1) in non-poultry birds was reported in Brazil between 6 April 2024 to 3 May 2024. ○ According to PAHO, there were seven outbreaks of avian influenza A(H5) in wild birds but no outbreaks in production birds or human cases between 1 January 2024 to 18 March 2024.
Cambodia	• Biology ○ Circulating clades ▪ 2.3.2.1c ○ Virological characteristics ▪ Infectivity/transmission ▪ Pathogenicity ▪ Virulence/disease severity • 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) ○ Susceptibility and transmission parameters ▪ Incubation period ▪ Clinical illness period ▪ Latent period ▪ Infectious period • Diagnosis ○ Molecular methods for rapid detection ○ Serological diagnostics (e.g., self-testing, point-of-care diagnostics) • Clinical presentation ○ Signs and symptoms	• As of 9 July 2024, Cambodia reported two additional human cases of A(H5N1) infections, raising the total number of cases in 2024 to seven. ○ The first new case was reported by Cambodia's ministry of health on 6 July 2024 and involved a three-year-old boy from the Takeo province who had symptoms of fever, coughing and difficulty breathing and was hospitalized; upon investigation, it was discovered that the boy had touched and held a chicken 10 days earlier that had died in the village. ○ The second new case was reported on 8 July 2024 and involved the five-year-old cousin of the first new case who lived in the same home and had reportedly also touched the dead chicken; the girl had mild symptoms and is receiving treatment. ○ The clade of A(H5N1) in these new cases is unknown. ○ In its 8 July 2024 announcement of the seventh reported case of human A(H5N1) infection in Cambodia, the Cambodian Ministry of Health highlighted that 10 of the 13 reported A(H5N1) cases in Cambodia over the last 18 months were in children, half of whom ended up passing away. • According to the ECDC, Cambodia has five confirmed cases of influenza A(H5N1) as of 12 March 2024. ○ Of the five cases, three have been confirmed to be infected with clade 2.3.2.1. ○ All individuals were in contact with sick or dead backyard poultry in their villages, with some having handled or consumed the poultry before the onset of symptoms. ○ Close contacts (except one individual) tested negative and were asymptomatic. • The Cambodia National Focal Point (NFP) for the International Health Regulations (IHR) notified the WHO between 26 and 28 January 2024 of two confirmed cases of human infection of avian influenza A(H5N1) virus; this was reported by WHO on 8 February 2024. ○ Samples of infected patients were tested at the National Institute of Public Health through quantitative reverse transcription polymerase chain reaction (RT-qPCR). ○ The U.S. CDC is working with the Cambodian government, the Wildlife Conservation Society of Cambodia, and the WHO in a One Health approach to respond to these human infections of avian influenza. • The first reported human infections with HPAI A(H5N1) virus in Cambodia in 2024 were identified in three children (one of whom died) and one adult in late January and early February.

Jurisdiction	Dimension of the organizing framework	Key findings
	○ Risk factors ○ Disease/illness course • Priority populations ○ Groups at higher risk of exposure ▪ Hunting and trapping wild birds and mammals (e.g., Indigenous harvesters) ▪ Working with live or recently killed poultry, cattle, or other livestock (e.g., butcher, processing plant worker, poultry culler)	○ All patients had a history of recent exposure to sick or dead poultry prior to becoming ill. ○ The first and second patients were admitted to different hospitals, and both recovered while the third and fourth patients were siblings but lived in different villages; the third patient died shortly after transfer to a paediatric hospital. ○ The H5 clade 2.3.2.1c of A(H5N1) was identified through genetic sequencing in the first and third patients; this clade was circulating in birds and poultry in Cambodia for several years.
Chile	• No relevant experiences reported from 1 February 2024 onwards.	• No new relevant experiences found between 14 May to 8 July 2024.
China	• Biology ○ Virological characteristics ▪ Infectivity/transmission ▪ Pathogenicity ▪ Virulence/disease severity • Epidemiology (including transmission) ○ Route of transmission ▪ Human to human ○ Susceptibility and transmission parameters ▪ Incubation period • Diagnosis ○ Serological diagnostics (e.g., self-testing, point-of-care diagnostics)	• The Chinese National Influenza Center routinely publishes weekly influenza reports. ○ One such report on 14 March 2024 reported a case of H5N6 avian influenza in a 59-year-old female in China, admitted on 29 November 2023 and reported to the WHO between 22 December 2023 to 26 February 2024. ○ One report from 4 July 2024 documented two cases of H5N6 avian influenza in Fujian Province, China, where both individuals had been exposed to poultry. ▪ One case involved a 52-year-old female who developed symptoms on 13 April, was hospitalized on 22 April, and died on 30 April. ▪ Another case involved a 41-year-old male who developed symptoms on 8 May, was hospitalized on 11 May, and died on the same day. ○ A report from 4 July 2024 documented a case of A(H5N1) in a 33-year-old female in China, an imported case from Vietnam, who developed mild symptoms on 26 March 2024 and had been exposed to poultry in Vietnam. • The ECDC report from March 2024 indicated that there was an additional confirmed case (in a 33-year old woman) in Sichuan where she was exposed to live birds at a live poultry market. ○ The woman had an underlying condition and died 26 days after developing symptoms. ○ According to the ECDC, Cambodia has five confirmed cases of H5N1 as of 12 March 2024.
Ecuador	• Epidemiology (including transmission) ○ Route of transmission ▪ Environmental viral load (e.g., avian and mammalian viral shedding) ○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution) • Diagnosis ○ Molecular methods for rapid detection • Priority populations ○ Groups at higher risk of exposure ▪ Working on a commercial poultry farm (e.g., producer, seasonal/migrant workers)	• No new relevant experiences found between 14 May to 8 July 2024. • In September 2023, there were reports of two new cases of HPAI in Ecuador in commercial and backyard flocks, with increases in mortality of the layer flocks being noted. ○ Samples of the flocks tested positive for an H5N1 variant, and control measures such as quarantine, disinfection, surveillance, and euthanizing of infected birds were put in place. ○ This report was last updated in April 2024. • The first reported human case of avian influenza A(H5N1) in Ecuador was reported to WHO on 9 January 2023 and involved a nine-year-old girl from Bolivar Province who developed severe symptoms and had to be hospitalized. ○ Upon investigation, it was discovered that a week before the girl's symptoms began, her family obtained poultry that died with no apparent cause on 19 December 2023. ○ A nasal sample from the patient tested positive for influenza A(H5) by RT-PCR on 7 January 2023.

Jurisdiction	Dimension of the organizing framework	Key findings
	▪ Working with non-commercial or backyard flocks ▪ Breeding and handling birds (e.g., dealer, breeder of exotics, falconry, racing pigeons)	
France	• Biology o Immunological characteristics ▪ Antigen/antibody and cellular immune responses (including cross-protection and cross-reactivity with other human influenza viruses, seasonal strains) • Epidemiology (including transmission) o Route of 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 o Serological diagnostics (e.g., self-testing, point-of-care diagnostics) • Clinical presentation o Signs and symptoms o Risk factors o Disease/illness course • Priority populations o Groups at higher risk of exposure ▪ Working on a commercial poultry farm (e.g., producer, seasonal/migrant workers) ▪ Working with non-commercial or backyard flocks • Breeding and handling birds (e.g., dealer, breeder of exotics, falconry, racing pigeons)	• On 4 July 2024, the European Food Safety Authority issued a statement indicating that avian flu cases are on the decline in Europe, with the lowest reported cases in poultry and wild birds since 2019–2020. • A total of 25 avian influenza outbreaks were confirmed between 1 October 2023 and 14 June 2024, which include 10 virus detections of A(H5N1) in poultry, and 11 A(H5N1) and four A(H5Nx) in wild birds; of these, only one new report of A(H5Nx) in wild birds (European herring gull) was reported between 16 March 2024 and 14 June 2024. o Two A(H5N1) outbreaks were noted in commercial establishments, affecting 4,000 and 13,770 turkeys; increased mortality and decreased food and water intake were identified upon infection. o Two outbreaks were noted in December in another housing establishment, affecting 9,660 and 303,700 turkeys; increased mortality and decreased food and water intake were identified upon infection. o In January 2024, an A(H5N1) was confirmed in a vaccinated Muscovy duck-housing establishment, affecting 8,700 ducks; two-dose vaccinated 74-day-old male ducks resided in the establishment, with the second dose given 41 days prior to the infection. ▪ Humoral immune response and virological protection data provided evidence to suggest that vaccine protection was reduced post–second dose with increasing age of the ducks. o In January 2024, another outbreak was detected, causing the death of 40 ducks and presenting clinical signs of neurological disorders, and decreased food and water intake. • Over 650 European clade 2.3.4.4b A(H5) viruses have been characterized, 90% of which belong to six different A(H5N1) and one A(H5N5) genotypes o One of these genotypes is EA-2022-BB (for the herring gull in France). • The French Agency for Food, Environmental and Occupational Health and Safety (ANSES) is committed to combating the spread against the disease by coordinating the diagnosis of avian influenza in animals and conducting research to improve virus detection. o ANSES's Ploufragan-Plouzané-Niort Laboratory is the National Reference Laboratory for avian influenza testing and diagnosis; standardized samples are sent to veterinary laboratories for RT-PCR testing with the Reference Library confirming any positive results. o In May 2022, ANSES partnered with the Ministry of Agriculture to engage in a pilot study/trial to assess the value of vaccinating ducks against the avian influenza and will inform the action plan for the region.
New Zealand	• No relevant experiences reported from 1 February 2024 onwards	• No new relevant experiences found between 14 May to 8 July 2024.
Spain	• No relevant experiences reported from 1 February 2024 onwards.	• A recent report published 28 June 2024 found another second case of avian influenza in a patiamarilla seagull this year.
United Kingdom	• Epidemiology o Reported cases and other epidemiological indicators of avian influenza A(H5Nx)	• No new relevant experiences reported between 14 May to 8 July 2024. • The U.K. does not currently have outbreaks of avian influenza in poultry or other captive birds and the current risk is low, but H5N1 continues to be found in wild birds in Great Britain and across Europe.

Jurisdiction	Dimension of the organizing framework	Key findings
	(e.g., prevalence, case fatality rates, geographic distribution)	○ The U.K. has self-declared zonal freedom from highly pathogenic avian influenza for Great Britain with effect from the 29 March 2024. ○ The U.K. is maintaining a live dashboard of findings of avian influenza in wild birds, however the numbers are cumulative (and cannot be sorted by year). ○ Since February 1, there have been eight cases of avian influenza found in wild birds across the U.K. and a mix of H5N1 and H5N5.
United States	• Biology ○ Circulating clades ▪ 2.3.4.4b ○ Epidemiology ▪ Bird to non-human mammal ▪ Non-human mammal to mammal ○ Reported cases and other epidemiological indicators of avian influenza (H5Nx) (e.g., prevalence, case fatality rates, geographic distribution) • Diagnosis ○ Molecular methods for rapid detection ○ Serological diagnostics (e.g., self-testing, point-of-care diagnostics) • Clinical presentation ○ Signs and symptoms ○ Risk factors	• As of 3 July 2024, an additional case H5N1 has been reported among humans in the U.S., leading to five total since 2022. ○ The latest case was identified in the state of Colorado following an ongoing multistate outbreak of A(H5N1) in dairy cows. ○ This is the first in Colorado, with the previous three taking place in Michigan (one case) and Texas (two cases). ○ The individual reported eye symptoms only, received oseltamivir treatment, and has since recovered. • The CDC has not changed the public health risk from low, given there remains no person-to-person spread. • The current public health risk is low given there has been no person-to-person spread, but there is ongoing multi-state outbreak among dairy cattle, widespread influenza among wild birds, and sporadic outbreaks among poultry flocks and mammals. • As of 5 July 2024, 12 states in the U.S. have now confirmed H5N1 clade 2.3.4.4b among 139 dairy cow herds. • A technical report updated on 5 June 2024 (the July update has not yet been released) notes that the CDC continues to actively work on clade 2.3.4.4b viruses and is performing ongoing analyses of the virus to identify genetic changes, but to date few genetic changes of public health concern have been identified in viruses circulating in wild birds and poultry. • The U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service provides regular updates on detections in dairy cattle and updated epidemiological reports and guidance for farmers and veterinarians. ○ As of 11 July 2024, the USDA reported 49 confirmed cases of H5N1 in dairy cattle herds in six states in the last 30 days. • On the 10 May 2024, the U.S. Food and Drug Administration reported that all 297 samples from an initial survey of retail dairy products were found to be negative for viable Highly Pathogenic H5N1 Avian Influenza. ○ An update on previous sampling survey is under way and testing an additional 155 dairy products for H5N1 at retail locations, including fluid milk and products such as aged raw milk cheese, pasteurized milk and pasteurized cheeses, cream cheese, butter, and ice cream.
Vietnam	• Epidemiology ○ Reported cases and other epidemiological indicators of avian influenza (H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)	• No new relevant experiences found between 14 May to 8 July 2024. • A confirmed human case (H5N1) was reported to the WHO on 25 March 2024. ○ The male patient developed fever and cough, abdominal pain and diarrhoea, which eventually led to the diagnosis of severe pneumonia, severe sepsis and acute respiratory distress syndrome. ○ The patient had been trapping wild birds and had reported no contact with dead or sick poultry. ○ The patient passed away on 23 March.

Appendix 7: Detailed jurisdictional scan about what is known about the emergence, transmission, and spectrum of the burden of disease of avian influenza A(H5Nx) subtypes in Canadian provinces and territories

Jurisdiction	Dimension of the organizing framework	Key findings
Pan-Canada	• Biology ○ Circulating clades ▪ 2.3.4.4b ▪ 2.3.2.1c • Diagnosis ○ Molecular methods for rapid detection ○ Serological diagnostics (e.g., self-testing, point-of-care diagnostics) • Priority populations ○ Groups at higher risk of exposure	• According to the Public Health Agency of Canada (PHAC), as of 10 July 2024, highly pathogenic avian influenza has not been detected in cattle or other livestock in Canada, and the risk of transmission to humans remains low. • The PHAC Human Emerging Respiratory Pathogens Bulletin recent monthly issue provided situational analysis of A(H5Nx) subtypes from global data reported for June 2024. ○ No human cases have been detected in Canada since November 2021. ○ The bulletin indicated one new human case of A(H5N6) during the month of June 2024. ○ As of 30 June 2024, there have been 11 human cases of A(H5N1) with one case in Australia, five in Cambodia, one in China, three in the United States, and one in Vietnam. ○ In May 2024, Mexico reported the first human case of A(H5N2), with the spectrum of the disease reported to be unknown. ○ One human case of A(H5N6) was reported in June 2024 in China (with now total of three cases, all in China), with onset illness on 8 May 2024 due to exposure to backyard poultry, and subsequently hospitalized with severe pneumonia and passing away. • In light of the recent detection of highly pathogenic avian influenza (HPAI) in unpasteurized milk of dairy cattle in the U.S., the Canadian Food Inspection Agency (CFIA) in collaboration with Health Canada and PHAC has been proactively testing commercial milk samples across Canada to detect fragments of the virus. ○ As of 18 June 2024, 600 retail milk samples from across Canada were tested for HPAI fragments and all samples tested negative. • On 6 June 2024, an assessment was completed on the risk scenario of influenza A(H5Nx) clade 2.3.4.4b virus and related viruses by PHAC, which found that cattle-to-cattle transmission of influenza A(H5Nx) clade 2.3.4.4b virus is occurring but transmission is complex, and concerns remain about the virus's ability to reassort; however, human-to-human transmission is not expected to occur in Canada in the next year. • On 19 April 2024, PHAC reported in a rapid risk assessment on avian influenza A(H5N1) clade 2.3.4.4b in livestock, developed due to the detection of this clade in cattle and goats in the U.S., that the likelihood of human infection with avian influenza A(H5N1) clade 2.3.4.4b in the next three months is very low. • The Canadian Animal Health Surveillance System (CAHSS) provides resources from national and international organizations on emerging public and food safety concerns, including reports from the Community for Emerging and Zoonotic Diseases and the National Collaborating Centre for Environmental Health.
British Columbia	• Biology ○ Virological characteristics ▪ Virulence/disease severity • Epidemiology (including transmission) ○ Route of transmission ▪ Bird/non-human mammal to human (i.e., zoonotic transmission)	• As of 10 July 2024, British Columbia has one active infected premise (confirmed by laboratory testing for the detection of H5N1), with a total of 157 previously infected premises since the start of the global outbreak, and has affected an estimated 6 million birds within the province. ○ Since 20 October 2023, the CFIA has confirmed 52 farms (47 commercial and five small flock) having been infected with H5N1, with the majority being in the Fraser Valley. ○ Human HPAI infection symptoms may range from asymptomatic to mild/severe illness (e.g., fever, fatigue, cough, headache, abdominal pain, nausea, shortness of breath, chest pain).

Jurisdiction	Dimension of the organizing framework	Key findings
	▪ Human to human o Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution) o Susceptibility and transmission parameters ▪ Incubation period • Diagnosis o Molecular methods for rapid detection • Clinical presentation o Signs and symptoms o Risk factors • Priority populations o Groups at higher risk of exposure ▪ Working on a commercial poultry farm (e.g., producer, seasonal/migrant workers) ▪ Working with non-commercial or backyard flocks ▪ Breeding and handling birds (e.g., dealer, breeder of exotics, falconry, racing pigeons) ▪ Hunting and trapping wild birds and mammals (e.g., Indigenous harvesters) ▪ Working in healthcare settings and other contacts of cases (if human-to-human transmission starts)	o HPAI testing can be completed through a nasopharyngeal and throat swabs within five days of symptom onset and specimens should be sent directly to the BC Centre for Disease Control (BCCDC) Public Health Laboratory. ▪ Testing method is nucleic acid testing; positive influenza A samples are subtyped using the H5 NAT assay. ▪ The BCCDC Medical Microbiologist should be notified of the case and testing request. ▪ Since April 2022, British Columbia's Animal Health Centre has tested nearly 45,000 samples for avian influenza.
Alberta	• Epidemiology (including transmission) o Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution) • Priority populations o Groups at higher risk of exposure ▪ Working on a commercial poultry farm (e.g., producer, seasonal/migrant workers) ▪ Working with non-commercial or backyard flocks	• No new relevant experiences found between 14 May to 8 July 2024. • The CFIA reported two outbreaks of H5N1 in 2024, with the first occurring in a non-commercial backyard poultry farm on 9 February and the second at a commercial poultry operation on 19 February.
Manitoba	• Epidemiology (including transmission) o Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g.,	• As of 10 July 2024, Manitoba has no infected premises, 23 previously infected premises, and an estimated 400 000 birds impacted to date. • As of April 3, 2024, the risk of Avian influenza during the 2024 spring wild bird migration remains high.

Jurisdiction	Dimension of the organizing framework	Key findings
	prevalence, case fatality rates, geographic distribution)	○ HPAI cases across Western Canada are currently active, with an increased risk during the spring and fall wild bird migration seasons.
Saskatchewan	• Epidemiology (including transmission) ○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)	• As of July 10, 2024, Saskatchewan has two infected premises, 42 previously infected premises, and an estimated 742,000 birds impacted to date.
Ontario	• Diagnosis ○ Molecular methods for rapid detection	• No new relevant experiences found between 14 May to 8 July 2024. • As of 10 May 2024, Public Health Ontario reported that there have been no laboratory-confirmed cases of influenza A(H5N1) in Ontario. • Public Health Ontario uses real-time PCR molecular tests to detect the presence of A(H5N1). • The CFIA has estimated that as of 10 April 2024, 899,000 birds in Ontario were impacted by HPAI.
Quebec	• Biology ○ Virological characteristics ▪ Infectivity/transmission ▪ Pathogenicity • 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) ○ Susceptibility and transmission parameters ▪ Incubation period • Clinical presentation ○ Signs and symptoms ○ Risk factors • Priority populations ○ Groups at higher risk of exposure ▪ Working on a commercial poultry farm (e.g., producer, processing plant worker, poultry culler), including seasonal/migrant workers ▪ Hunting and trapping wild birds and mammals (e.g., Indigenous harvesters) ▪ Working in healthcare settings and other contacts of cases (if human-to-human transmission starts)	• As of 10 July 2024, Quebec has no active infected premise of H5N1, with a total of 54 previously infected premises since the start of the outbreak, and has affected an estimated 1.4 million birds within the province. • The Government of Quebec has reported the H5N1 virus circulating as of April 2022, affecting wild birds across all regions within the province. ○ In Quebec, only the poultry sector has been affected and no cases have been detected within cattle or other livestock. ○ A range of measures have been implemented within the province to ensure that cows and the milk consumed is safe, including the ban on isolating poultry in a dairy barn, the exclusion of milk from sick animals during milking and pasteurization. ○ The risk of avian flu for the general population remains low. ▪ No case of transmission/sustained transmission of the disease to humans has been noted. • Clinical symptoms among birds affected by the disease include: ○ A lack of energy and food intake ○ decreased egg production ○ shell-less eggs ○ soft-shelled eggs ○ swelling of the head, eyelids, comb, and wattles ○ coughing ○ sneezing ○ diarrhoea ○ stiff neck. • The incubation period is two to 14 days in length, and is transmitted directly from one bird to another through secretions and droppings. • Disease transmission occurs through infected domestic or wild birds, infected individuals, contaminated materials/surfaces/food/water supplies, vermin, and offsprings.

Jurisdiction	Dimension of the organizing framework	Key findings
New Brunswick	• Epidemiology (including transmission) ○ Route of transmission ▪ Bird to non-human mammal ▪ Non-human mammal to mammal (including development of a non-human mammal reservoir, bovines and other ruminants) ▪ Bird/non-human mammal to human (i.e., zoonotic transmission) ○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)	• The CFIA national avian influenza dashboard has not reported any new positive or suspected cases of HPAI in birds or mammals from January 2024 to July 11 2024. • The Canadian federal government page on the status of ongoing avian influenza response by province has not been updated since the previous version of this living evidence profile and continues to report an estimated number of under 100 birds affected by HPAI in New Brunswick, with two previously infected premises and without specification of strain as of 10 April 2024. • The Government of New Brunswick website has an undated advisory notice regarding avian influenza. ○ The notice specifies the difference in pathogenicity of avian influenza and contains disposal guideline for dead wild birds that does not fall in line with other provincial/territorial guidelines for reducing contact with potentially infectious wild birds.
Newfoundland and Labrador	• No relevant experiences reported from 1 February 2024 onwards	• No new relevant experiences found between 14 May to 8 July 2024.
Nova Scotia	• Epidemiology (including transmission) ○ Route of transmission ▪ Bird to non-human mammal ▪ Non-human mammal to mammal (including development of a non-human mammal reservoir, bovines and other ruminants) ▪ 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) • Clinical presentation ○ Signs and symptoms	• The Canadian federal government page on the status of ongoing avian influenza response by province has not been updated since the previous version of this living evidence profile and continues to report an estimated number of 12,000 birds affected by HPAI in Nova Scotia without specification of strain as of 10 April 2024. • The CFIA national avian influenza dashboard has reported a total of 17 new positive and suspect cases of HPAI A(H5Nx) across both birds and mammals as of July 11 2024, concentrated in coastal areas. ○ Recently authorized positives (authorized April–June 2024, collected March–May 2024) display H5N5 and H5N1 strains. • Lineage is either fully Eurasian (all gene segments belonging to Eurasian lineage) or Reassortment EU&NA (gene segments PB2, PB1 and PA belonging to North American lineage and gene segments HA, NP, NA, M, and NS belonging to Eurasian lineage). • The Nova Scotia government website has a short article and a visual fact sheet on avian influenza. ○ The article contains symptoms for humans and specifies that the virus can be transmitted through direct contact with an infected bird or a contaminated surface. ○ There are no cases of human infection with avian influenza in Nova Scotia currently. ○ The fact sheet displays clinical signs for birds as well as biosecurity measures to limit transmission. ○ There is an active infected premises designated February 2024 in Lunenburg Country Nova Scotia PCZ-232. ▪ The area includes both commercial and non-commercial poultry.
Prince Edward Island	• Epidemiology (including transmission) ○ Route of transmission ○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution) ○ Susceptibility and transmission parameters ▪ Incubation period • Clinical presentation	• The CFIA national avian influenza dashboard has reported a total of three new positive and suspect cases of HPAI appearing only in mammals (specifically the red fox) as of July 11 2024, concentrated in coastal areas. ○ Recently authorized positives (authorized May 2024, collected April and May 2024) display A(H5Nx) and H5N1 strains. • Lineage is fully Eurasian (all gene segments belonging to Eurasian lineage). The P.E.I. government website edited a previous published article on avian influenza on June 21 2024, which focuses on the current outbreak of HPAI H5N1.

Jurisdiction	Dimension of the organizing framework	Key findings
	○ Signs and symptoms	○ This page focuses specifically on symptoms in birds, the incubation period of two to 14 days, and transmissibility between wild waterfowl and domestic or farmed birds (e.g., backyard flocks). ○ Strict biosecurity practices are needed in order for commercial poultry producers to prevent the spread to their livestock. ▪ Wild waterfowl can carry the virus without any signs of illness and are considered the major reservoir for AI infections in domestic poultry. ▪ Small flocks in Atlantic Canada that have been infected with this virus have commonly had watercourses on their property. ○ The page specifies transmission to humans has occurred when people have had close contact with infected birds or heavily contaminated environments, but risk remains low. ○ The page mentions transmission from birds to livestock and provides links to federal government resources on HPAI in livestock. ○ The page mentions that the CFIA has not detected HPAI in retail Canadian milk, dairy cattle, or other livestock in Canada.
Northwest Territories	• Epidemiology (including transmission) ○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)	• No new relevant experiences reported between 14 May to 8 July 2024.
Yukon	• Epidemiology (including transmission) ○ Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)	• No new relevant experiences reported between 14 May to 8 July 2024.
Nunavut	• Epidemiology (including transmission) ○ Route of transmission • Priority populations ○ Groups at higher risk of exposure ▪ Working on a commercial poultry farm (e.g., producer, processing plant worker, poultry culler), including seasonal/migrant workers ▪ Working with non-commercial or backyard flocks ▪ Breeding and handling birds (e.g., dealer, breeder of exotics, falconry, racing pigeons) ▪ Hunting and trapping wild birds and mammals (e.g., Indigenous harvesters)	• No new relevant experiences reported between 14 May to 8 July 2024.

Appendix 8: Key list of sources for identifying relevant technical reports and documents in other countries and Canada

Jurisdiction	Key sources
International organizations	• WHO, FAO, WOAH joint assessment • European Food Safety Authority • European Centre for Disease Control and Prevention – Weekly Bulletins • WHO Influenza at the human-animal interface summary and assessment • WAHIS: World Animal Health Information System
Australia	• Wildlife Health Australia • Health Direct Australia
Brazil	• WHO, FAO, WOAH joint assessment • WAHIS: World Animal Health Information System
Cambodia	• U.S. Centers for Disease Control and Prevention and Cambodia • Avian influenza overview December 2023–March 2024
Canada	• Government of Canada • Public Health Agency of Canada • Canadian Food Inspection Agency • Canadian Food Inspection Agency – H5Nx wildlife dashboard (in collaboration with Environment and Climate Change Canada and Canadian Wildlife Health Cooperative) • Canadian Food Inspection Agency – HPAI detection across provinces • Canadian Food Inspection Agency – Guidance for cattle and livestock • Canadian Animal Health Surveillance System • Government of British Columbia • BC Centre for Disease Control • Government of Alberta • Government of Saskatchewan • Government of Manitoba • Public Health Ontario • Avian Influenza (Quebec) • Government of New Brunswick • Government of Newfoundland • Nova Scotia • Prince Edward Island • Northwest Territories • Yukon • Nunavut
Chile	• Ministerio de Salud • Servicio Nacional de Pesca y Acuicultura

Jurisdiction	Key sources
China	• European Centre for Disease Control and Prevention – Weekly Bulletins • Chinese Center for Disease Control and Prevention
Ecuador	• WAHIS: World Animal Health Information System
France	• European Centre for Disease Control and Prevention – Weekly Bulletins • Ministry of Agriculture and Food Sovereignty
New Zealand	• Ministry of Primary Industries • Department of Conservation • Health New Zealand
Spain	• Centro de Coordinación de Alertas y Emergencias Sanitarias • WHO – Spain
United Kingdom	• U.K. Health Security Agency – Bird flu (avian influenza): Latest situation in England • Animal & Plant Health Agency • NHS – Bird Flu • Department for Environment, Food & Rural Affairs
United States	• U.S. Centers for Disease Control and Prevention • USDA Animal and Plant Health Inspection Service • Updates on HPAI – U.S. Food & Drug Administration
Vietnam	• WHO, FAO, WOAH joint assessment • WAHIS: World Animal Health Information System

Appendix 9: Documents excluded at the final stages of reviewing

Document type	Hyperlinked title
Evidence syntheses	Nurses' coping strategies caring for patients during severe viral pandemics: A mixed-methods systematic review
	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	Bird flu outbreak in dairy cows is widespread, raising public health concerns
	Epidemiology, biosafety, and biosecurity of avian influenza: Insights from the east mediterranean region
	Highly pathogenic avian influenza A(H5N1) virus infection in a dairy farm worker
	Highly pathogenic avian influenza H5N1 virus infections of dairy cattle and livestock handlers in the United States of America
	Molecular markers and mechanisms of influenza A virus cross-species transmission and new host adaptation
	The alarming situation of highly pathogenic avian influenza viruses in 2019–2023
	Zoonotic infections by avian influenza virus: Changing global epidemiology, investigation, and control
	Concerns on H5N1 avian influenza given the outbreak in U.S. dairy cattle
	Emerging threats in public health: H5N1 transmission from dairy cattle to humans
	As a third worker tests positive for bird flu in us dairy cattle outbreak, here's what to know
	CDC: H5N1 bird flu confirmed in person exposed to cattle
	Highly pathogenic avian influenza (HPAI) h5 clade 2.3.4.4b virus infection in birds and mammals
	Potential zoonotic spillover at the human–animal interface: A mini-review
	Transboundary determinants of avian zoonotic infectious diseases: Challenges for strengthening research capacity and connecting surveillance networks
	Insights from avian influenza: A review of its multifaceted nature and future pandemic preparedness
	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

Document type	Hyperlinked title
	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	A tool for prioritizing livestock disease threats to Scotland
	An overview of transboundary animal diseases of viral origin in South Asia: What needs to be done?
	Avian influenza A viruses modulate the cellular cytoskeleton during infection of mammalian hosts

Document type	Hyperlinked title
	Backyard poultry: Exploring non-intensive production systems
	Bird flu outbreak in us cows: Why scientists are concerned
	Common and potential emerging foodborne viruses: A comprehensive review
	Comparative investigation of coincident single nucleotide polymorphisms underlying avian influenza viruses in chickens and ducks
	Disease control tools to secure animal and public health in a densely populated world
	Emerging threats: Is highly pathogenic avian influenza A(H5N1) in dairy herds a prelude to a new pandemic?
	Highly pathogenic avian influenza H5N1 virus infection of companion animals
	Highly sensitive and label-free detection of influenza H5N1 viral proteins using affinity peptide and porous BSA/MXENE nanocomposite electrode
	Interactions between avian viruses and skin in farm birds
	Mechanisms of intestinal epithelial cell damage by *clostridium perfringens*
	Molecular detection of avian influenza virus in wild birds in Morocco, 2016–2019
	Respiratory disease complex due to mixed viral infections in chicken in Jordan
	Safety and immunogenicity of a delayed heterologous avian influenza A(H7N9) vaccine boost following different priming regimens: a randomized clinical trial
	Signalling and responding to zoonotic threats using a one health approach: A decade of the zoonoses structure in the Netherlands, 2011 to 2021
	Study of the interface between wild bird populations and poultry and their potential role in the spread of avian influenza
	The public health importance and management of infectious poultry diseases in smallholder systems in Africa
	U.S. dairy farm worker infected as bird flu spreads to cows in five states
	Viral RNA capping: Mechanisms and antiviral therapy
	Zoonotic animal influenza virus and potential mixing vessel hosts
	Optimizing environmental viral surveillance: Bovine serum albumin increases RT-qPCR sensitivity for high pathogenicity avian influenza H5Nx virus detection from dust samples
	Association between movement patterns, microbiome diversity, and potential pathogen presence in free-ranging feral pigeons foraging in dairy farms
	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

Document type	Hyperlinked title
	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
Pre-prints	Detection of novel influenza viruses through community and healthcare testing: Implications for surveillance efforts in the United States
	Detection of hemagglutinin H5 influenza A virus sequence in municipal wastewater solids at wastewater treatment plants with increases in influenza A in spring, 2024
	Sustained vaccine exposure elicits more rapid, consistent, and broad humoral immune responses to multivalent influenza vaccines
	Virome sequencing identifies H5N1 avian influenza in wastewater from nine cities
	Pandemic risk assessment for a swine influenza A virus in comparative human substrates (H1)
	Potential pandemic risk of circulating swine H1N2 influenza viruses
	Detection of clade 2.3.4.4b highly pathogenic H5N1 influenza virus in New York City
	Effects of cattle on vector-borne disease risk to humans: A systematic review
Commentaries	Highly pathogenic avian influenza A (H5N1) virus infection in a dairy farm worker
	A bird flu vaccine for cows? It's complicated.
	Avian influenza in cattle in the USA

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