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.

## Context

- Avian influenza A(H5Nx) viruses have been reported globally, leading to large outbreaks in poultry and wild birds, and sporadic detections among mammals.
- Recent H5 viruses (clades 2.3.4.4b and 2.3.2.1c) have emerged or re-emerged, causing concern about the potential transmission and spectrum of the burden of disease in humans.
- More recently, a multi-state outbreak of avian influenza A(H5N1) in dairy cows was reported on 25 March 2024 in the U.S., which has been noted as being reflective of the continued spread of clade 2.3.4.4b viruses that entered the U.S. in late 2021.(1;2)
- There have been confirmed human cases of A(H5Nx) subtypes globally in 2024 (including 14 cases of A(H5N1), one case of A(H5N2), and two cases of A(H5N6) as of 9 July 2024), leading to ongoing surveillance and monitoring of the situation.(1-5)
- This living evidence profile (LEP) was originally requested to identify the state of evidence and knowledge gaps from existing evidence syntheses related to the emergence, transmission, and spectrum of the burden of disease in humans of avian influenza as a first step to informing prevention and mitigation interventions.
- A subsequent update (LEP 7.2) was focused on identifying any existing evidence syntheses published since the initial searches conducted on 18 December 2023, as well as single studies that we could identify about transmission involving cattle or other ruminants and transmission risk to livestock workers, given the recent outbreak in the U.S.
- The previous LEP update (7.3) included searches for evidence documents using the same scope as the last version (as outlined in the previous point), and the addition of a new jurisdictional scan to provide more detailed insights from other countries and Canadian provinces and territories about the emergence, transmission, and spectrum of the burden of avian influenza A(H5Nx) subtypes.
- This LEP (7.4) provides an update to the searches and jurisdictional scan since the last version, documenting any new insights from 14 May 2024 to the week of 8 July 2024.

### Box 1: Evidence and other types of information

**+ Global evidence drawn upon**

Evidence syntheses selected based on relevance, quality, and recency of search

**- Forms of domestic evidence used (🍁= Canadian)**

Evaluation

**- Other types of information used**

| Jurisdictional scan | 12 countries (AU, BR, CB, CI, CH, EC, FR, NZ, SP, UK, US, VM), in addition to international organizations and Canadian provinces and territories |
|---|---|

*** Additional notable features**

Prepared in three business days using an ‘all hands on deck’ approach

## Question

- What is known about the emergence, transmission (including spillover potential), and spectrum of the burden of disease in humans of avian influenza A(H5Nx) subtypes currently circulating and emerging in existing evidence documents and from experiences in other jurisdictions?

## High-level summary of new key findings

- We identified eight new evidence documents (two evidence syntheses and six single studies) since the last update of this LEP
    - With these newly identified evidence documents, we have included a total of 38 evidence documents (24 evidence syntheses and 14 single studies).
- We conducted a jurisdictional scan of select countries (Australia, Brazil, Cambodia, Chile, China, Ecuador, France, New Zealand, Spain, United Kingdom, United States, and Vietnam), international organizations (World Health Organization (WHO), Pan American Health Organization (PAHO), World Organisation for Animal Health (WOAH), European Centre for Disease Prevention and Control (ECDC), and the Food and Agriculture Organization (FAO)), and Canadian provinces and territories to identify any relevant publicly available information and experiences with A(H5Nx).
- Canada and the other countries scanned continue to report no evidence of human-to-human transmission and indicate that the overall public health risk for the general public is low.
- The transmission of A(H5N1) to different animal populations 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.

### Box 2: Approach and supporting materials

At the beginning of each living evidence profile and throughout its development, we engage a subject matter expert, who helps us to scope the question and ensures 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 syntheses and protocols for evidence syntheses 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). We also conducted a search for single studies in PubMed and the USDA National Agricultural Library relevant only to dairy cattle, other non-human mammals (including ruminants), transmission associated with dairy products, and risk to livestock (and not a more comprehensive search for all single studies about avian influenza). The searches were not limited by publication date except in PubMed, which was limited to literature published from the last five years (2019 onwards). In addition, we re-ran searches for pre-prints in medRxiv and bioRxiv from 14 May 2024 to 8 July 2024. The search strategies used are included in Appendix 1.

We hand searched government and stakeholder websites of other select countries (Australia, Brazil, Cambodia, Chile, China, Ecuador, France, New Zealand, Spain, United Kingdom, United States, and Vietnam), international organizations (WHO, PAHO, WOAH, ECDC, and FAO), and Canadian provinces and territories to identify any publicly available information published since 14 May 2024 to the week of 8 July 2024. A list of sources is included in Appendix 8.

In contrast to synthesis methods that provide an in-depth understanding of the evidence, this profile focuses on providing an overview and key insights from relevant documents. Note that the timing, frequency, and scope of future updates of this LEP will be determined in collaboration with the requestor.

A separate appendix document includes:
1) methodological details (Appendix 1)
2) details about evidence documents and jurisdiction scans (Appendices 2–7)
3) key list of sources for jurisdictions (Appendix 8)
4) documents excluded at final stage of review (Appendix 9)

This update to the living evidence profile was prepared in the equivalent of three day of a ‘full court press’ by all involved staff.

- There are new confirmed human cases of A(H5Nx) subtypes, including the first case in Australia (clade 2.3.2.1a of A(H5N1), Cambodia (A(H5N1)), U.S. (clade 2.3.4.4b of A(H5N1)), China (A(H5N1) and A(H5N6)), and Vietnam (A(H5N1)) in 2024.
- While it is not within the select countries for the jurisdictional scan, a notable finding was the first confirmed human case of A(H5N2) in Mexico reported in the June 2024 Human Emerging Respiratory Pathogens Bulletin by the Public Health Agency of Canada (PHAC).
- International organizations and jurisdictions continue to recommend ongoing surveillance and collaboration to understand the biology and epidemiology of A(H5Nx) viruses.

## Framework to organize what we looked for

- Biology
  - Circulating clades
    - 2.3.4.4b
    - 2.3.2.1c
    - Other (if new subtypes identified as having emerged)
  - Genomic changes and impacts
    - Infectivity/transmission
    - Pathogenicity
    - Virulence/disease severity
    - Mammalian adaptation
    - Antiviral susceptibility
  - Virological characteristics
    - Infectivity/transmission
    - Pathogenicity
    - Virulence/disease severity
  - 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)
  - 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)
    - 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)
  - Susceptibility and transmission parameters
    - Incubation period
    - Clinical illness period
    - Latent period
    - Infectious period
    - Virus shedding
- Diagnosis
  - Molecular methods for rapid detection
  - Serological diagnostics (e.g., self-testing, point-of-care diagnostics)

- Clinical presentation
    - Signs and symptoms
    - Risk factors
    - Disease/illness course
- Priority human populations
    - 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
        - Livestock farm worker/small herd owner
        - 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 with live or recently killed poultry, cattle, or other livestock (e.g., butcher, processing plant worker, poultry culler)
        - Working with unpasteurized milk products (e.g., milk processing plant worker, cheesemaker)
        - Veterinarians and veterinary staff
        - 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 with non-human mammals that commonly eat wild birds
        - Working or visiting live bird or mammal markets
        - Working with or caretaking of animals that regularly interact with wild birds (e.g., caretakers, pets, guardian dogs, hunting dogs, mink/fur animal farmer)
        - Working in healthcare settings and other contacts of cases (if human-to-human transmission starts)
    - Other equity considerations

## What we found

Since the last update of this LEP we identified eight new evidence documents (two evidence syntheses and six single studies from evidence searches conducted on 8 July 2024). With these newly identified evidence documents, we have included a total of 38 evidence documents (24 evidence syntheses and 14 single studies).

### Gaps in existing evidence documents

There continues to be limited but growing available evidence on the emergence, transmission, and spectrum of the burden of avian influenza A(H5Nx) subtypes. Similar to the previous version of this LEP, the evidence documents emphasized the importance of continued surveillance of avian influenza viruses among domestic production animals to understand virus evolution and pathogenesis and to prevent cross-species and mammal-to-mammal transmission.

### What existing evidence tells us about the emergence, transmission, and spectrum of the burden of disease in humans of avian influenza A(H5Nx)

*General A(H5Nx) subtypes*

The identified evidence syntheses described the biology, epidemiology, diagnosis, and clinical presentation of avian influenza A(H5Nx). In terms of biology (virological characteristics), a medium-quality evidence synthesis reported on transmission dynamics largely focusing on domestic poultry as the epidemiological unit and with all of the studies, except five, focusing on highly pathogenic avian influenza (HPAI). The authors suggested that most transmission between poultry farms occurred within a short to medium distance range to each other regardless of subtype or geographical location. The authors reported a reproduction number ranging from 0.03–15.7 for between-farm transmission in poultry of A(H5N1).(6) A low-quality evidence synthesis found that HPAI virus shedding was higher than that of low pathogenic avian influenza virus (LPAI). For the introduction routes of HPAI viruses, intranasal or intraconal routes resulted in no difference in shedding compared to infection by contact. Overall, virus shedding levels among poultry largely depend on the introduction routes (e.g., intranasal, aerosol, oropharyngeal).(7) Finally, a single study (pre-print) found that avian influenza A(H5N1) 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.(8)

Related to epidemiology, nine evidence syntheses described the prevalence, route of transmission, and susceptibility parameters among birds, non-human mammals, and humans. Three low-quality evidence syntheses (one conducted in 2018, one in 2019, and one did not specify the search date but was published in 2023) described the prevalence in birds from different regions around the world. In Sub-Saharan Africa, the authors reported an overall 3.0% prevalence, with A(H5N1) being the most frequently observed, followed by A(H5N2) and A(H5N8) among both wild and domestic birds (particularly in chickens and ducks).(9) According to the authors, Indigenous African bird species and migratory water birds from Eurasia keep avian influenza viruses in circulation. Further, they indicated that A(H5N1) HPAI viruses were widespread in this region due to being a major wintering destination for migratory water birds.(9) In China, it was found that waterfowl were considered the most important transmitters of avian influenza viruses (including the A(H5Nx) subtypes); however, the prevalence in wild birds varied by region.(10) One low-quality evidence synthesis reported a combined global prevalence of 1.6% of A(H5N8) among birds.(11) We found one low-quality evidence synthesis that described the prevalence of A(H5N1) in humans. In Egypt, it was found that most A(H5N1) human-infection cases were among children, younger adults, and those with direct exposure to poultry.(12) Two medium-quality and two low-quality evidence syntheses described other routes of transmission and susceptibility parameters. One evidence synthesis found the movement of birds, humans and fomites all play a role in transmitting HPAI viruses among birds and between humans and birds during poultry production (e.g., live bird movements between farms, chick movements from hatchery, bird pick-up to slaughter for broiler production, feed delivery, egg collection, human movement such as contact from veterinarians or farm workers).(13) Another evidence synthesis described the risk of interspecies transmission from backyard farms that involve both domestic poultry and swine.(14) However, one evidence synthesis found that the role of backyard farms in transmission was minimal.(6) Authors in another evidence synthesis highlighted the importance for studies to contextualize the species and subtypes to have a better understanding of transmission and risk.(15) Finally, a medium-quality evidence synthesis that conducted literature searches in October 2023 indicated that ongoing challenges with A(H5N1) have significantly impacted biodiversity and mammalian health as there are an increasing number of infected mammal species, as well as probable non-human mammal-to-mammal transmission. The authors of the evidence synthesis underscored the importance of continuous surveillance and international collaboration.(16)

A single study published in May 2024 reported that birds within urban areas of New York have confirmed cases of A(H5N1), which prompted the authors to recommend urban-based surveillance programs particularly in high density areas where there may be an increased chance of being in contact with infected birds.(17)

Related to the diagnosis of avian influenza A(H5Nx), three evidence syntheses (one low-quality and two medium-quality) indicated that promising techniques largely involve sample collections from live birds at markets and farms (e.g., swabs, serology), dead birds (e.g., swabs, organ samples) and the environment (e.g., feces, mud, feeding sources, feathers and air, surfaces likely contaminated with viruses such as cages, chopping boards, defeathering machines, trucks, boots).(18-20)

For clinical presentation, a low-quality evidence synthesis indicated that all reported cases of A(H5N6) in humans had prior contact with birds and were found to have a high disease severity, with 95% of cases resulting in hospitalization. Most of reported contact methods included visits to live bird markets, employment as a poultry worker, and direct exposure to recently killed poultry.(21)

One medium-quality evidence synthesis indicated that LPAI A(H5) typically caused mild clinical symptoms among poultry. However, HPAI viruses like A(H5N2), A(H5N6), and A(H5N8) were described to cause severe morbidity and mortality in poultry.(6)

#### *Clade 2.3.4.4b*

We identified limited insights about clade 2.3.4.4b from evidence syntheses. Relevant evidence identified is primarily based on epidemiological findings in China, the Western Pacific Region, and North America. In terms of biology, a medium-quality evidence synthesis indicated that the increasing presence of influenza A viruses among poultry and wild bird habitats within various water environments warrants the need for standardized protocols and increased research in underrepresented regions.(22) In terms of epidemiology, one medium-quality evidence synthesis found that the overall seroprevalence of A(H5N1) infection among humans was 2.45% in China, with a higher seroprevalence in Central China (7.3%).(23) A low-quality evidence synthesis indicated that the risk of zoonotic transmission is low in Western Pacific Region, despite changes in primary subtypes and frequency of reported cases.(24) A recent medium-quality evidence synthesis (literature last searched 28 May 2024) reported that the spread of A(H5N1) clade 2.3.4.4b is likely attributed to the migration of birds. The prevalence of disease in non-bird species is low.(25) A recent low-quality evidence synthesis (literature last searched 2023) indicated that the transmission risk to the general public and beachgoers is low.(26) Another low-quality evidence synthesis found that this particular clade was found among wild birds in Alaska, and the authors concluded that these wild birds likely contributed to outbreaks among wild and domestic birds in Canada and the United States in recent years.(27)

We also identified one low-quality evidence synthesis that found that people with poultry exposures (e.g., poultry workers and cullers) had higher seroprevalence of A(H5N1) antibodies than non-poultry exposed people. There were low frequencies of antibodies detected among close contacts of confirmed A(H5N1) cases.(28)

One newly identified single study (pre-print) confirmed that the A(H5N1) clade 2.3.4.4b caused the deaths of five south polar skuas (a type of seabird) in Antarctica.(29) Another new single study reported the circulation of a new genotype B3.13 of clade A(H5N1) 2.3.4.4b among dairy cattle after amino acid mutations associated with mammalian adaptations indicated approximately four months of evolution with limited local circulation in dairy cattle in the United States.(30) The study highlighted that the detection of low-frequency sequence variants could pose a potential zoonotic threat of increased interspecies transmission.

#### *Clade 2.3.2.1c*

We found limited information on clade 2.3.2.1c in the identified evidence syntheses. Two medium-quality evidence syntheses reported that this particular clade was found in domestic poultry and dead birds in Cameroon in addition to African pigs in Nigeria.(31;32) The authors indicated that there could be potential transmission to other mammals, emphasizing the need for improved surveillance in Africa. Additionally, clade 2.3.2.1c was mentioned briefly in a low-quality evidence synthesis, where they described the low risk of zoonotic transmission in the Western Pacific Region.(24)

#### *Insights about cattle and other ruminants*

In terms of the biology of avian influenza A(H5Nx), a low-quality evidence synthesis reported that the evolution and host adaptation of influenza A viruses in bovine species had been hindered until the emergence of novel influenza D virus in cattle, as some bovine host factors with potential anti-influenza properties may have provided influenza A virus resilience for bovines.(33) In addition, a single study (pre-print) reported that influenza A virus receptors found in humans, ducks, and chickens were widely expressed in the bovine mammary gland and respiratory tract, which may explain the high levels of A(H5N1) virus in infected bovine milk. The authors expressed their concerns regarding the possibility of new genomic changes occurring within influenza A virus.(34) A study published in June 2024 reported that the European lineage HPAI A(H5N1) has the ability to cause infection and proliferate in bovine epithelial cells, similar to the North American lineage HPAI A(H5N1).(35) The authors of another single study (pre-print) from May 2024 concluded that infected cows may shed virus for two to three weeks. The study also found amino acid mutations associated with mammalian adaptation, indicating four months of evolution with limited local circulation in dairy cattle. Low-frequency sequence variants among the infected cows were also detected, which may lead to the increased probability of phenotypes that may increase interspecies transmission.(30)

Epidemiological features of avian influenza A(H5Nx) transmission were discussed in the eight single studies that we identified from our focused search on outbreaks in cattle and other ruminants. According to one study by the U.S. Centers for Disease Control and Prevention (CDC), dairy cattle farms reported cow-to-cow transmission of A(H5N1).(1) The reported incidence was four to six days after the first animals were affected and then tapered off between 10 and 14 days in March 2024. The affected cows experienced apparent systemic illness, an abrupt drop in milk production, reduced feed intake and rumination, and the production of thick, yellow milk. The study indicated that ingestion of feed contaminated with feces from wild birds is presumed to be the most likely initial source of infection in the dairy cows. This study and two recently published studies from July 2024 concluded that A(H5N1) can be shed in milk, which could lead to cross-species and mammal-to-mammal transmission via unpasteurized milk.(36;37) The authors of recent study conducted in Texas, U.S. reported transmission among cattle, with high genetic similarity between the virus strain in cattle, birds and humans, which suggests a single interconnected multispecies outbreak in Texas.(38) A recent study (pre-print) in Canada that tested retail milk samples for the presence of H5 RNA from all 10 provinces were found to be negative.(39)

Wild waterfowl was identified in a study as a potential transmission pathway for avian influenza in livestock (including cows) on commercial facilities, and it was noted that natural or artificial water and food sources in or near facilities reportedly increased the likelihood of attracting these birds.(40) A newly identified single study (pre-print) indicated that non-waterfowl species had the highest dairy farm exposure, and additional factors such as livestock trade, the use of poultry litter that may contain excrement and/or feathers along with bedding from poultry farms, and contaminated milking machinery may have led to the amplification of the outbreaks in the U.S.(41) The outbreak in the U.S. has been reportedly clustered within the clade 2.3.4.4b new genotype B3.13 and a recent single study (pre-print) suggests that this new genotype could pose as a potential zoonotic threat, requiring continued monitoring to inform epidemiological risk and early warning for any interspecies transmission. The new genotype B3.13 may have resulted from the recent reassortment events.(30)

Finally, one report noted that while Europe and North America continued to see widespread outbreaks of avian influenza A(H5Nx) in domestic and wild birds between December 2023 and March 2024, North America remained a hotspot for outbreaks in poultry.(42) The report also noted that goat kids in the U.S. were infected with influenza A(H5N1) virus in 20 March 2024, which represents the first reported infection in any ruminant species worldwide.

## Key findings from the jurisdictional scan

Key findings from the jurisdictional scan that was updated on 8 July 2024 from the previous scan that was conducted on 14 May 2024 are summarized below according to each of the categories in the organizing framework.

### *Biology*

Some international organizations and countries reported on the circulating clades. In a joint assessment released on 23 April 2024 by the WHO, FAO, and WOAH, the entities indicated that 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. A technical report updated on 26 April 2024 notes that the U.S. 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 A(H5N1) was identified through genetic sequencing in two confirmed human cases in

Cambodia. This clade has been circulating in birds and poultry in Cambodia and Vietnam for several years. In France, they confirmed A(H5N1) infection among farmed Muscovy ducks that had two doses of vaccination. The second dose was given 41 days prior to 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*

Avian influenza A(H5Nx) continues to be monitored across international organizations, countries, and Canadian provinces and territories analyzed in our jurisdiction scans. According to PAHO, WHO, ECDC, EFSA, U.S. CDC, and PHAC, the overall risk to the public remains low. Additionally, the WHO Western Pacific region's weekly report on A(H5N1) and A(H5N6) (5 to 11 July 2024) indicates the overall pandemic risk has not significantly changed in comparison to previous years. The organizations recommend ongoing surveillance of the global situation. The transmission of A(H5N1) to different animal populations 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.

There have been confirmed human cases of A(H5Nx) globally. The June 2024 Human Emerging Respiratory Pathogens Bulletin from PHAC reported that between 13 January 2024 to 30 June 2024 there were 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, and the first ever reported human case of A(H5N2) in Mexico. Australia's first human case of A(H5N1) 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 2024, and intensive care unit transfer on 4 March 2024. A nasopharyngeal swab and endotracheal aspirate taken on 6 and 7 March 2024 initially tested positive for influenza A and were later confirmed as A(H5N1) clade 2.3.2.1a which is different from the main A(H5N1) clade currently circulating worldwide in animals, including in Canada. The child is now reported to be clinically well. The child had no known exposure to sick persons or animals during her stay, and their close family contacts in Australia or India did not develop symptoms as of 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.

New human cases of A(H5N1) have been confirmed since the release of the June 2024 PHAC bulletin. As of 9 July 2024, Cambodia reported two additional human cases of A(H5N1) infections, raising the total number of cases in Cambodia 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. His condition was reported to be improving. Upon investigation, it was discovered that the boy had been in contact with a deceased chicken 10 days prior to the onset of his illness. 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 had contact with the chicken that died. The girl had mild symptoms and was receiving treatment at the time of the report. The clade of A(H5N1) in these new cases is currently unknown. Additionally, the Cambodian Ministry of Health highlighted most cases this year have been among children.

In the U.S., there have now 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.

One report from 4 July 2024 documented two cases of A(H5N6) avian influenza in Fujian Province, China, where both individuals had been exposed to poultry. The first case involved a 52-year-old female who developed symptoms on 13 April 2024, who was hospitalized on 22 April 2024, and subsequently died on 30 April 2024. The other 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 terms of birds, poultry continues to remain at risk from the continued circulation and spillover of A(H5N1) viruses from wild birds. The ECDC weekly bulletin reported new recurrences of A(H5N1) in poultry and non-poultry birds. The U.K. has self-declared zonal freedom from highly pathogenic avian influenza 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, but A(H5N1) continues to be found in wild birds in the U.K. and across Europe. Since 1 February 2024, there have been eight cases of avian influenza found in wild birds across the U.K., which include a mix of A(H5N1) and A(H5N5). France confirmed A(H5N1) in a vaccinated Muscovy duck-housing establishment, affecting 8,700 ducks in January 2024. 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. According to PAHO, there were seven outbreaks of avian influenza A(H5) in wild birds in Brazil but no outbreaks in production birds or human cases between 1 January 2024 to 18 March 2024. Since then, an outbreak of A(H5N1) in non-poultry birds was detected in Brazil between 6 April 2024 to 3 May 2024. The Canadian Food Inspection Agency (CFIA) reports on the number of infected poultry flocks where A(H5N1) has been detected in Canada. Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, Quebec, and Saskatchewan have reported flocks infected with HPAI A(H5N1) since September 2023.

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 infection in ferrets has led to severe disease. The CFIA in collaboration with Environment and Climate Change Canada (ECCC) and the Canadian Wildlife Health Cooperative (CWHC) have a dashboard where they monitor A(H5Nx) in different types of wildlife. As of February 2024, there have been confirmed cases of either A(H5N1), A(H5), A(H5N5) or a combination across all the provinces and territories. Between 14 May to July 11 2024, the dashboard reported a total of three new positive A(H5Nx) and A(H5N1) cases appearing in red foxes, which were concentrated in coastal areas in Prince Edward Island.

In terms of cattle and other ruminants, the joint assessment by the WHO, FAO, and WOAH reported A(H5N1) detection in dairy cattle in the U.S and in neonatal goats (that shared space on a farm with A(H5N1) infected poultry). 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 A(H5N1) clade 2.3.4.4b among 139 dairy cow herds. The U.S. CDC reported that there have been four reported human cases following exposure to dairy cattle. The outbreak in dairy cows is multi-state and was first reported on 25 March 2024. Lateral transmission among dairy cattle on affected premises in the U.S. is likely occurring. Currently, there are reports that A(H5N1) has spread from dairy cattle back into some poultry premises; however, the transmission route and frequency of cattle-to-bird transmission is unknown. As of 20 April 2024, no markers of mammalian adaptation have been found in the avian influenza A(H5N1) virus isolated from infected dairy cattle. A technical report updated on 5 June 2024 (the July update has not yet been released at the time of writing this report) 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. While public health risk is low, the ongoing multi-state outbreak among dairy cattle and widespread influenza infection among wild birds and sporadic outbreaks among poultry flocks and mammals are concerning.

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 and Drug Administration (FDA) completed 297 retail dairy samples, and all were found negative as of 10 May 2024. The ECDC weekly bulletin reported no cases in cattle in Europe as of 3 May 2024. According to PHAC, as of 16 May 2024, highly pathogenic avian influenza A(H5N1) has not been detected in cattle or livestock (apart from poultry) in Canada, and the risk of transmission to humans remains low. Additionally, the CFIA in collaboration with Health Canada and PHAC have been proactively testing commercial milk samples across Canada to detect fragments of the A(H5N1) virus. As of 14 May 2024, all tested samples have been negative. On 6 June 2024, a PHAC assessment on the risk scenario of avian influenza A(H5Nx) clade 2.3.4.4b virus and related viruses found that cattle-to-cattle transmission of avian influenza A(H5N1) clade 2.3.4.4b virus is occurring, but transmission is complex, and concerns remain about the virus's ability to reassort.

### *Diagnosis*

There are common testing methods such as RT-PCR and ELISA that are being applied across the jurisdictions for A(H5Nx). For example, 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 A(H5N1) virus in livestock for state animal health officials, veterinarians, and producers. The WOAH indicated that A(H5Nx) in non-avian species (including cattle and other livestock populations) should be 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 A(H5Nx) in birds or cattle. 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 of the disease by coordinating the diagnosis of avian influenza in animals and conducting research to improve virus detection. The BC Centre for Disease Control uses nucleic acid testing and Public Health Ontario uses RT-PCR to detect the presence of A(H5N1).

### *Clinical presentation*

There are existing reports on the clinical presentation of A(H5Nx) in humans, birds, and non-human mammals. 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. The following findings about clinical presentation are from the previous versions of LEP (with new information on the cases under the Epidemiology section). Countries such as Cambodia, Vietnam, and China reported deaths due to complications. In Cambodia, all confirmed human cases were hospitalized with symptoms, and the person who died was admitted when their conditions worsened. The weekly report by ECDC from 28 April to 4 May 2024 reported the symptoms of one case in Cambodia, including cough, difficulty breathing, and fever, who was eventually treated with the antiviral oseltamivir. In Vietnam, the human case who was eventually admitted had fever, cough, abdominal pain, and diarrhea. The patient's condition worsened to severe pneumonia, severe sepsis, and acute respiratory distress syndrome. The patient eventually died eight days after being admitted to the hospital in March 2024. From the 12 March 2024 ECDC report, China reported that two cases of A(H5N6) developed severe symptoms, with one death 26 days after developing symptoms. In the A(H5N1) case with exposure to dairy cattle in the U.S., the patient was diagnosed with conjunctivitis and subconjunctival hemorrhage.

In terms of birds, clinical signs can 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. For example, 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 a sudden drop in 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. As with previous versions of the LEP, the confirmed human cases (including children) were those in close contact with or handling suspected or confirmed infected cattle and birds (e.g., poultry markets and backyard poultry, wild birds).

## Next steps

Additional next steps should focus on efforts to fill gaps in the literature, which include:

- evidence syntheses on the biology (genomic changes, virological characteristic) with clear descriptions of the circulating clades (including different characteristics)
- evidence syntheses on susceptibility and transmission parameters among birds, non-human mammals (e.g., cattle or other livestock), and humans
- evidence syntheses on diagnosis and clinical presentation (including disease severity) of avian influenza A(H5Nx) categorized by birds, non-human mammals, and humans
- evidence syntheses with clear descriptions of the population groups and regions, particularly among those at higher risk of exposure
- primary studies that further investigate transmission of avian influenza in cattle and other livestock species, as well as to livestock workers, given the recent outbreak in the U.S. and limited number of primary studies identified from our searches on this topic
- jurisdictional scans that continue to monitor and understand the current state of A(H5Nx) around the world, especially to identify technical reports on the emerging biology and priority populations.

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