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

2 May 2024

[MHF product code: LEP 7.2]

Box 1: Evidence and other types of information

+ Global evidence drawn

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

- Forms of domestic evidence used (🍁 = Canadian)

🍁 Evaluation

*** Additional notable features**

Update prepared in one business day using an ‘all hands on deck’ approach

Context

- Avian influenza A (H5Nx) viruses have been reported globally, leading to large outbreaks in poultry, wild birds and mammals.
- Recent H5 viruses (clades 2.3.4.4b and 2.3.2.1c) have emerged or re-emerged, causing concern on the potential transmission and spectrum of the burden of disease in humans.
- More recently, a multi-state outbreak of highly pathogenic 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)
- The U.S. CDC has since confirmed one human H5N1 infection and while there is uncertainty about whether the infection was due to exposure to dairy cattle in Texas with presumed infection or contaminated environment, this is likely the first instance of mammal-to-human transmission.(1-4)
- 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.
- This updated version of the LEP was focused on identifying any existing evidence syntheses published since the initial searches were conducted on 18 December 2023, as well as single studies that we could identify about transmission involving cattle or other ruminants, as well as transmission risk to livestock workers, given the recent outbreak in the U.S.
- The LEP does not include a jurisdictional scan, but expansions in scope may be made in future to include single studies in other priority areas and/or a jurisdictional scan to provide more detailed insights to support ongoing work towards informing prevention and mitigation interventions.

Questions

- 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?

High-level summary of key findings

- We identified nine new evidence documents (six evidence syntheses and three single studies that provide insight about avian influenza in cattle and other ruminants) since the last update to understand the emergence, transmission and spectrum of the burden of disease of avian influenza A (H5Nx) subtypes.
- This LEP also includes evidence documents from the previous version that we deemed to be relevant, for a total of 25 evidence syntheses that provided insights about avian influenza A (H5Nx), plus the three newly identified single studies.
- New evidence documents supplement previous findings about the epidemiology and biology of H5Nx and provide added insight about circulating clades and transmission involving cattle or other ruminants.
- Some evidence reported that clade 2.3.2.1c was found in domestic poultry and dead birds in Cameroon and in African pigs in Nigeria.
- In terms of clade 2.3.4.4b, some authors reported 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.
- Cow-to-cow transmission of avian influenza A (H5N1) was found in the U.S. in March 2024, which has negatively impacted milk production and quality.
- The findings suggest cross-species and non-human mammal-to-mammal transmission of H5N1.
- The authors of the evidence documents on cattle and other

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.

We identified evidence addressing the question by searching ACCESSSS, Health Systems Evidence, Health Evidence and PubMed for full evidence syntheses (or synthesis-derived products such as overviews of evidence syntheses) and protocols for evidence syntheses. These searches were last conducted on 1 May 2024 and were not limited by publication date except in PubMed, which was limited to literature published from the last five years (2019 onwards). We also conducted a search for single studies in PubMed and the USDA National Agricultural Library relevant to the outbreak in dairy cows. We also included evidence syntheses and single studies relevant to the outbreak in dairy cows in the U.S. identified from internal searches provided by the Public Health Agency of Canada (PHAC) that were conducted for literature published since October 2022 with the last search conducted on 13 December 2023. The search strategies used are included in Appendix 1.

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 and that, while single studies and jurisdictional scans have not yet been prioritized for inclusion in this LEP, they may be included in future enhanced versions.

We appraised the methodological quality of evidence syntheses that were deemed to be highly relevant using the first version of the AMSTAR tool. AMSTAR rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality, medium-quality evidence syntheses are those with scores between four and seven, and low-quality evidence syntheses are those with scores less than four. The AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to evidence syntheses pertaining to delivery, financial or governance arrangements within health systems or implementation strategies.

A separate appendix document includes:

1) methodological details (Appendix 1)
2) details from evidence documents organized by circulating clade (Appendix 2)
3) details about each identified evidence synthesis (Appendix 3)
4) details about each identified single study (Appendix 4)
5) documents that were excluded in the final stages of review (Appendix 5).

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

ruminants reported that natural or artificial water and food sources in or near the facilities may have increased the likelihood of attracting wild birds that could act as transmission pathways.

- We continue to find limited evidence on the burden of disease in humans.
- Included evidence emphasized continued surveillance of highly pathogenic avian influenza viruses among domestic production animals to understand virus evolution, pathogenesis and to prevent cross-species and non-human mammal-to-mammal transmission.
- Additional next steps should focus on efforts to fill gaps in the literature such as generation of evidence syntheses on the biology of circulating clades, susceptibility and transmission parameters, diagnosis and clinical presentation across species (birds, non-human mammals, humans), and clear descriptions of priority population groups.

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 on:
    - Infectivity/transmission
    - Pathogenicity
    - Virulence/disease severity
    - Mammalian adaptation
    - Antiviral susceptibility
  - Virological characteristics
    - Infectivity/transmission (i.e., likelihood to infect a host)
    - Pathogenicity (i.e., ability to cause disease)
    - Virulence/disease severity
- Epidemiology (including transmission)
  - 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)
    - 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
  - Immunological characteristics
    - Innate

        - Adaptive
        - Antigen/antibody and cellular immune responses
- Priority populations
    - Groups at higher risk of exposure
        - Working on a commercial poultry farm (e.g., producer, processing plant worker, poultry culler)
        - 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 with live or recently killed poultry (e.g., butcher)
        - Working with wild birds and/or mammals for healthcare, research and conservation (e.g., veterinarians, 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
        - Livestock farm worker/small herd owner
        - Meat/milk processing plant worker
        - Working with or caretaking of animals that regularly interact with wild birds (e.g., caretakers, pets, guardian dogs, hunting dogs, mink farmer)
        - Working in healthcare settings and other contacts of cases (if human-to-human transmission starts)
    - Other equity considerations

What we found

We identified nine new evidence documents (six evidence syntheses and three single studies that provide insight about avian influenza in cattle and other ruminants) since the last update of this LEP. This LEP also includes evidence documents from the previous version that we deemed to be relevant, for a total of 25 evidence syntheses that provided insights about avian influenza A (H5Nx), plus the three newly identified single studies. The new evidence documents supplement what was previously found about the epidemiology and biology of H5Nx and provides further insight about the circulating clades and the outbreak in cattle and other ruminants. Additionally, four evidence documents (one evidence synthesis and three single studies) provided insights specifically about the outbreak in dairy cows, which we summarize in the last sub-section below.(1; 5-7)

Many evidence documents were excluded (but are listed in Appendix 4), largely because they were literature reviews without an explicit search strategy. The methodological details of the living evidence profile can be found in Box 1 and Appendix 1. We describe below the gaps and findings from the evidence syntheses with additional details about each of the included evidence syntheses and single studies provided in Appendix 3 and 4 respectively.

Gaps in existing evidence syntheses

We found several gaps in existing evidence syntheses. Most of the evidence syntheses described H5Nx subtypes in general, but they did not explicitly describe the circulating clades (2.3.4.4b and 2.3.2.1c) or other emerging subtypes. Overall, we found limited evidence about the biology, epidemiology, diagnosis, clinical presentation in general or specific to priority populations or across H5Nx subtypes and clades. Some reasons could be due to the focus on evidence syntheses for this version, the indexing of avian influenza A literature in the bibliographic databases (e.g., mostly literature reviews with no methods section), and limited detailed descriptions within the identified evidence syntheses. Within the identified literature, authors described key evidence gaps about poultry production and networks, sample techniques, contextual factors and parameters that influence transmission and risks across species, and approaches to developing optimal avian influenza surveillance programs.(8-23)

For the priority update about evidence with insights about transmission related to dairy cows, the evidence documents emphasized the importance of continued surveillance of highly pathogenic avian influenza viruses among domestic production animals to understand virus evolution, pathogenesis and to prevent cross-species and mammal-to-mammal transmission.

What existing evidence syntheses tell us about the emergence, transmission and spectrum of the burden of disease in humans of influenza A

General 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 individual birds as the epidemiological unit. The authors suggested that most HPAI 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 H5N1.(19) A low-quality evidence synthesis found that HPAI virus shedding was higher than that of low pathogenicity 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).(14)

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 described the prevalence in birds from different regions around the world. In Sub-Saharan Africa, the authors reported an overall 3.0% prevalence, with H5N1 being the most frequently observed, followed by H5N2 and H5N8 among both wild and domestic birds (particularly in chickens and ducks).(17) According to the authors, Indigenous African bird species and migratory water birds from Eurasia keep avian influenza viruses in circulation. Further, they indicated that H5N1 HPAI viruses were widespread in this region due to being a major wintering destination for migratory water birds.(17) In China, it was found that waterfowl were considered the most important transmitters of avian influenza viruses (including the 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 H5N8 among birds.(8) We found one low-quality evidence synthesis that described the prevalence of H5N1 in humans. In Egypt, it was found that most H5N1 human-infection cases were among children, younger adults and those with direct exposure to poultry.(21) 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).(15) Another evidence synthesis described the risk of interspecies transmission from backyard farms that involve both domestic poultry and swine.(9) However, one evidence synthesis found that the role of backyard farms in transmission was minimal.(19) 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.(18) Finally, a medium-quality evidence synthesis indicated that ongoing challenges with H5N1 have significantly impacted biodiversity and mammalian health as there are an increasing number of infected mammal species, as well as non-human mammal-to-mammal transmission. The authors of the evidence synthesis underscored the importance of continuous surveillance and international collaboration.(24)

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 and serology), dead birds (e.g., swabs and/or organ samples) and the environment (e.g., feces, mud, feeding sources, feathers and air and surfaces likely contaminated with viruses such as cages, chopping boards, defeathering machines, trucks and boots).(12; 16; 20)

For clinical presentation, a low-quality evidence synthesis indicated that 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. Most of reported contact methods included visits to live bird markets, employment as a poultry worker, and direct exposure to recently killed poultry.(25)

One medium-quality evidence synthesis indicated that LPAI H5 typically caused mild clinical symptoms among poultry. However, HPAI viruses like H5N2, H5N6, H5N8 were described to cause severe morbidity and mortality in poultry.(19)

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.(26) In terms of epidemiology, one medium-quality evidence synthesis found that the overall seroprevalence of H5N1 infection among humans was 2.45% in China, with a higher seroprevalence in Central China (7.3%).(22) 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.(23) 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.(13)

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 H5N1 antibodies than non-poultry exposed people. There were low frequencies of antibodies detected among close contacts of confirmed H5N1 cases.(11)

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.(27; 28) 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 as low.(23)

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 virus 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.(6)

Epidemiological features of avian influenza A (H5Nx) transmission were discussed in the three 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, dairy cattle farms reported cow-to-cow transmission of 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. 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. The study concluded that H5N1 can shed virus in milk, which could lead to cross-species and mammal-to-mammal transmission via unpasteurized milk. While the study indicated that the exact source of the virus is unknown, migratory birds (Anseriformes and Charadriiformes) were considered potential sources. Wild waterfowl were identified in another 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.(7)

Finally, one study found 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.(5) The study reported that goat kids in the U.S. were infected with influenza A (H5N1) virus, which was noted as representing the first natural infection in any ruminant species worldwide. In addition, the study noted that there is higher risk of transmission from ruminant species to humans in close contact with them, but they did not find any evidence of sustained human-to-human transmission.

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 characteristics) 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 ruminants), and humans
- evidence syntheses on diagnosis and clinical presentation 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 ruminant 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.

References

1. Burrough ER, Magstadt DR, Petersen B, et al. Highly Pathogenic Avian Influenza A (H5N1) Clade 2.3. 4.4 b virus infection in domestic dairy cattle and cats, United States, 2024. *Emerging infectious diseases*;30(7).
2. U.S. Centers for Disease Control and Prevention. Current H5N1 bird flu situation in dairy cows. Atlanta, GA: 2024. https://www.cdc.gov/flu/avianflu/mammals.htm (accessed.
3. Harris E. CDC: H5N1 Bird flu confirmed in person exposed to cattle. *JAMA* 2024.
4. Looi M-K. Bird flu: Person with rare strain in US sparks alarm about cow transmission. *BMJ* 2024;385: q797.
5. Fusaro A, Gonzales JL, Kuiken T, et al. Avian influenza overview December 2023-March 2024. *Efsa j* 2024;22(3): e8754.
6. Sreenivasan CC, Thomas M, Kaushik RS, Wang D, Li F. Influenza a in bovine species: a narrative literature review. *Viruses* 2019;11(6): 561.
7. McDuie F, Matchett EL, Prosser DJ, et al. Pathways for avian influenza virus spread: GPS reveals wild waterfowl in commercial livestock facilities and connectivity with the natural wetland landscape. *Transboundary and Emerging Diseases* 2022;69(5): 2898-2912.
8. Calle-Hernández DM, Hoyos-Salazar V, Bonilla-Aldana DK. Prevalence of the H5N8 influenza virus in birds: Systematic review with meta-analysis. *Travel Med Infect Dis* 2023;51: 102490.
9. Chauhan RP, Gordon ML. A systematic review of influenza A virus prevalence and transmission dynamics in backyard swine populations globally. *Porcine Health Management* 2022;8(1): 10.
10. Chen X, Li C, Sun H-T, Ma J, Qi Y, Qin S-Y. Prevalence of avian influenza viruses and their associated antibodies in wild birds in China: A systematic review and meta-analysis. *Microbial Pathogenesis* 2019;135: 103613.
11. Chen X, Wang W, Wang Y, et al. Serological evidence of human infections with highly pathogenic avian influenza A(H5N1) virus: a systematic review and meta-analysis. *BMC Med* 2020;18(1): 377.
12. Coombe M, Iwasawa S, Byers KA, et al. A systematic review and narrative synthesis of the use of environmental samples for the surveillance of avian influenza viruses in wild waterbirds. *The Journal of Wildlife Diseases* 2021;57(1): 1-18.
13. Gass JD, Jr., Kellogg HK, Hill NJ, Puryear WB, Nutter FB, Runstadler JA. Epidemiology and Ecology of Influenza A Viruses among Wildlife in the Arctic. *Viruses* 2022;14(7).
14. Germeraad EA, Sanders P, Hagenaars TJ, Jong MCM, Beerens N, Gonzales JL. Virus shedding of avian influenza in poultry: a systematic review and meta-analysis. *Viruses* 2019;11(9).
15. Hautefeuille C, Dauphin G, Peyre M. Knowledge and remaining gaps on the role of animal and human movements in the poultry production and trade networks in the global spread of avian influenza viruses - A scoping review. *PLoS One* 2020;15(3): e0230567.
16. Hood G, Roche X, Brioudes A, et al. A literature review of the use of environmental sampling in the surveillance of avian influenza viruses. *Transboundary and Emerging Diseases* 2021;68(1): 110-126.
17. Kalonda A, Saasa N, Nkhoma P, et al. Avian influenza viruses detected in birds in sub-saharan africa: a systematic review. *Viruses* 2020;12(9).
18. Kirkeby C, Ward MP. A review of estimated transmission parameters for the spread of avian influenza viruses. *Transboundary and Emerging Diseases* 2022;69(6): 3238-3246.
19. Lambert S, Bauzile B, Mugnier A, Durand B, Vergne T, Paul MC. A systematic review of mechanistic models used to study avian influenza virus transmission and control. *Veterinary Research* 2023;54(1): 96.

20. Ntakiyisumba E, Lee S, Park BY, Tae HJ, Won G. Prevalence, seroprevalence and risk factors of avian influenza in wild bird populations in korea: a systematic review and meta-analysis. *Viruses* 2023;15(2).

21. Philippon DAM, Wu P, Cowling BJ, Lau EHY. Avian Influenza Human Infections at the Human-Animal Interface. *The Journal of Infectious Diseases* 2020;222(4): 528-537.

22. Qi Y, Ni HB, Chen X, Li S. Seroprevalence of highly pathogenic avian influenza (H5N1) virus infection among humans in mainland China: A systematic review and meta-analysis. *Transbound Emerg Dis* 2020;67(5): 1861-1871.

23. Skufca J, Bell L, Molino JP, et al. An epidemiological overview of human infections with HxNy avian influenza in the Western Pacific Region, 2003–2022. *Western Pacific Surveillance and Response Journal: WPSAR* 2022;13(4): 1.

24. Plaza PI, Gamarra-Toledo V, Euguí JR, Lambertucci SA. Recent changes in patterns of mammal infection with highly pathogenic avian influenza a(h5n1) virus worldwide. *Emerg Infect Dis* 2024;30(3): 444-452.

25. Sandhu S, Ferrante C, MacCosham A, Atchessi N, Bancej C. Epidemiological characteristics of human infections with avian influenza A(H5N6) virus, China and Laos: A multiple case descriptive analysis, February 2014-June 2023. *Can Commun Dis Rep* 2024;50(1-2): 77-85.

26. Kenmoe S, Takuissu GR, Ebogo-Belobo JT, et al. A systematic review of influenza virus in water environments across human, poultry, and wild bird habitats. *Water Res X* 2024;22: 100210.

27. Tahmo NB, Wirsiy FS, Nnamdi D-B, et al. An epidemiological synthesis of emerging and re-emerging zoonotic disease threats in Cameroon, 2000–2022: a systematic review. *IJID Regions* 2023;7: 84-109.

28. Kalonda A, Phonera M, Saasa N, et al. Influenza a and d viruses in non-human mammalian hosts in africa: a systematic review and meta-analysis. *Viruses* 2021;13(12): 2411.

Bhuiya A, Bain T, Waddell K, Ali A, DeMaio P, Moat K, Wilson MG. Living evidence profile 7.2: Examining what is known about the emergence, transmission and spectrum of the burden of disease of avian influenza A (H5Nx) subtypes. Hamilton: McMaster Health Forum, 2 May 2024.

This living evidence profile was funded by the Public Health Agency of Canada. The McMaster Health Forum receives both financial and in-kind support from McMaster University. The views expressed in the living evidence profile are the views of the authors and should not be taken to represent the views of the Public Health Agency of Canada or McMaster University. The authors wish to thank Angela Wang, Ariana Jaspal, Yao Maclean, and Tresha Sivanesanathan for conducting the AMSTAR appraisals.