

Appendices

- 1) Methodological details (Appendix 1)
- 2) Key findings from identified evidence documents (Appendix 2)
- 3) Detailed findings from identified synthesis (Appendix 3)
- 4) Documents that were excluded in the final stages of review (Appendix 4)

Identifying features and impacts of public health strategies that can be used to prevent, reduce and/or mitigate avian influenza spillover to humans

12 January 2024

[MHF product code: REP 64]

Appendix 1: Methodological details

We use a standard protocol for preparing rapid evidence profiles (REP) 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.

At the beginning of each rapid evidence profile 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.

Identifying research evidence

For this REP, we searched ACCESSSS, Health Systems Evidence, Health Evidence and [PubMed](#) using the following combination of terms: (avian influenza) OR (H5N1 or AH5N1 or A?H5N1 or H5Nx or H5N*). The searches were not limited by publication date except in PubMed, which was limited to literature published from the last five years (2019 onwards). In addition, we reviewed literature compiled from searches that were last conducted by the Public Health Agency of Canada (PHAC) on 13 December 2023. These detailed search strategies are available upon request. 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.

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

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

Assessing relevance and quality of evidence

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

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

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

Preparing the profile

Each included document is cited in the reference list at the end of the REP. 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). In this REP, we drafted the summary based on all evidence syntheses identified given that limited number included.

Upon completion, the REP is sent to the subject matter expert for their review.

Appendix 2: High-level findings from evidence documents, organized by public health strategy

Public health strategies	Features	Impacts or Outcomes	Priority populations
Information and education provision	The sharing of production and trade data between private and public sectors within commercial poultry networks can help to facilitate data access and inform policies to mitigate the global spread of avian influenza (AMSTAR rating 4/9; literature last searched 2019) Infection training for front-line healthcare workers, particularly those involved in endotracheal intubations, can significantly reduce their risk of infection (AMSTAR rating 8/11; literature last searched 2020)	Limited access to production and trade data for public researchers presents a crucial barrier to informing surveillance and control strategies within commercial poultry production and trade networks (AMSTAR rating 4/9; literature last searched 2019) Some barriers to delivering adequate infection training for front-line healthcare workers include constantly changing guidelines, poor communication and enforcement of guidelines, and increased workload and fatigue of healthcare workers (AMSTAR rating 8/11; literature last searched 2020)	Groups working in healthcare settings and other contacts of cases
Non-pharmaceutical public health strategies to prevent infection	<i>Using personal protective equipment (e.g., masks, gloves)</i> Protective measures (e.g., gloves, gowns, surgical masks, N95 respirators) for front-line healthcare workers, particularly those involved in endotracheal intubations, can significantly reduce their risk of infection (AMSTAR rating 8/11; literature last searched 2020) <i>Physical distancing</i> School closures were found to be one of the most commonly studied non-pharmaceutical public health strategies for major infectious disease threats (AMSTAR rating 4/9; literature last searched 2018) <i>Farm and market biosecurity measures</i> Live poultry market interventions to decrease incidence of avian influenza viruses include quarantine access systems, physically separating poultry from different sources, disinfection and decontamination, daily cleaning, rest days and live poultry market closures (AMSTAR rating 7/11; literature last searched 9 November 2018)	Closures were found to be the most effective live poultry market intervention to decrease incidence of avian influenza viruses; however, the effect of such interventions were not found to be statistically significant (AMSTAR rating 4/9; literature last searched 2018) Protective measures (e.g., gloves, gowns, surgical masks, N95 respirators) for front-line healthcare workers, particularly those involved in endotracheal intubations, can significantly reduce their risk of infection (AMSTAR rating 8/11; literature last searched 2020)	Groups working in healthcare settings and other contacts of cases
Pharmaceutical measures	<i>Vaccinations in humans</i> An Andalusian Agency for Health Technology Assessment reported that an inactivated split-virion formulation of the pre-pandemic H5N1 influenza vaccines that includes a low antigen dose and an oil-in-water emulsion-based adjuvant had a favourable safety	Oil-in-water emulsion-adjuvanted H5N1 vaccine were found to be effective at boosting an immune response to the H5N1 influenza virus (AMSTAR rating 6/11; literature last searched 31 January 2020) Additional research is needed to understand the reduced immune responses to H5N1 vaccination in individuals	None identified

Public health strategies	Features	Impacts or Outcomes	Priority populations
	profile and immunogenicity (AMSTAR rating 5/9; literature last searched 2009) • Two doses of 7.5µg of oil-in-water emulsion-adjuvanted H5N1 vaccine induced a robust antibody response and was well-tolerated among older adults (61 years and older) (AMSTAR rating 6/11; literature last searched 31 January 2020) • Adjuvanted H7N9 vaccines for humans were found to be immunogenic and safe in healthy individuals (AMSTAR rating 7/11; literature last searched 2017) <i>Vaccinations in animals</i> • A meta-analysis was conducted on studies that focused on both inactivated and recombinant fowlpox virus expressing H5 vaccines to determine outcomes for H5N1 and H5N2 avian influenza viruses among chickens (AMSTAR rating 5/11; published 2010)	who have received the seasonal influenza vaccine (AMSTAR rating 3/11; literature last searched 2012) • Adjuvanted H7N9 vaccines for humans were found to be immunogenic and safe in healthy individuals (AMSTAR rating 7/11; literature last searched 2017) <i>Vaccinations in animals</i> • While vaccines were efficacious to protect chickens from morbidity and mortality, virus shedding may be a biosecurity issue for future avian influenza outbreaks (AMSTAR rating 5/11; published 2010) • Among chickens, recombinant herpesvirus of turkeys (rHVT) and inactivated replicating viral-vectored offer advantages to induce broader immunity as they are more tolerant of variation in the hemagglutinin 1 domain (HA1) (AMSTAR rating 5/11; published 25 May 2022)	

Appendix 3: Detailed findings from evidence documents sorted by relevance

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
- Public health strategies - Pharmaceutical measures used as part of public health strategies - Vaccinations (in humans)	Individuals who have received seasonal influenza vaccine (SIV) within the past season or two may have reduced immune responses to H5N1 influenza A vaccination, but additional research is needed to understand the factors contributing to these diminished immune responses	High	No	3/11 (rating by McMaster Health Forum)	2012	No	None identified
- Public health strategies - Pharmaceutical measures used as part of public health strategies - Vaccinations (in humans) - Priority populations - Other equity considerations	Two doses of 7.5µg of oil-in-water emulsion-adjuvanted H5N1 vaccine induced a robust antibody response and was well-tolerated among older adults (61 years and older) - Inactivated virus vaccines were used in the ten identified studies, which elicited an antibody response among older adults (61 years and older) after two immunizations of H5N1 vaccines (ranging between 33–88%). - Two doses resulted in a higher antibody response than one dose. - The 7.5µg and 15 µg of MF59-adjuvanted vaccines and all doses of AS03-adjuvanted vaccines induced robust antibody responses among older adults. - Adverse reactions were mild and self-limiting.	High	No	6/11 (rating by McMaster Health Forum)	31 January 2020	No	None identified
- Public health strategies - Non-pharmaceutical public health strategies to prevent infection - Farm and market biosecurity measures	Live poultry market interventions (e.g., closures, physical separation of poultry from different sources) decreased incidence of avian influenza viruses (including H5 strains) and detection rates; however, the small sample size increased the risk of bias especially in retail or wholesale poultry samples - Live poultry market interventions included quarantine access systems, physically separating poultry from different sources, disinfection and decontamination, daily cleaning, rest days, and live poultry market closures. - Closures were found to have the highest effect among avian influenza viruses generally.	High	No	7/11 (rating by McMaster Health Forum)	9 November 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
	Particular to H5 influenza strain, there were lower detection rates of avian influenza virus after live poultry market interventions, but it was not statistically significant.						
- Public health strategies - Pharmaceutical measures used as part of public health strategies - Vaccinations (in humans)	The authors from the Andalusian Agency for Health Technology Assessment reported that an inactivated split-virion formulation of the pre-pandemic H5N1 influenza vaccines that includes a low antigen dose and an oil-in-water emulsion-based adjuvant had a favourable safety profile and immunogenicity - The authors reported that the vaccine was clinically acceptable. - The authors indicated that an internationally accepted anti-H5 clade 1 antiserum standard is needed and a priority.	High	No	5/9 (rating by McMaster Health Forum)	2009	No	None identified
- Public health strategies - Information and education provision - Non-pharmaceutical public health strategies to prevent infection - Farm and market biosecurity measures - Non-pharmaceutical measures public health strategies to control the spread of infections - Case and contact management - Isolation and quarantine - Border-control measures - Pharmaceutical measures used as part of public health strategies - Vaccinations (in animals) - Vaccinations (in humans) - Antiviral medications - Surveillance and reporting - Priority populations	Collaboration between private and public sectors to facilitate data access is needed to better understand animal, human and fomite movements within commercial poultry production and trade networks to help inform policy to mitigate global spread of avian influenza Limited access to production and trade data for public researchers presents a crucial barrier to informing surveillance and control strategies.	Medium	No	4/9 (rating by McMaster Health Forum)	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
○ Groups at higher risk of exposure ▪ Working on a commercial poultry farm (e.g., producers, processing plant worker, poultry culler) ▪ Breeding and handling birds (e.g., dealer, breeder of exotics, falconry, racing pigeons) ▪ Working or visiting live bird or mammal markets • Outcomes ○ Zoonotic infections							
• Public health strategies ○ Information and education provision ○ Non-pharmaceutical public health strategies to prevent infection ▪ Using protective equipment (e.g., masks, gloves) ▪ Washing hands • Priority populations ○ Groups at higher risk of exposure ▪ Working in healthcare settings and other contacts of cases (if human-to-human transmission starts) • Outcomes ○ Human-to-human infections	Front-line healthcare workers, particularly those involved in endotracheal intubations, face an increased risk of infection during respiratory pandemics, but protective measures such as gloves, gowns, surgical masks, N95 respirators, face protection and infection training significantly reduces the risk of infection • The delivery of adequate infection training faces barriers such as constantly changing guidelines, poor communication and enforcement of guidelines, and increased workload and fatigue of healthcare workers.	Low	No	8/11 (rating by McMaster Health Forum)	2020	Yes	None identified
• Public health strategies ○ Information and education provision	One study in the systematic review focused on H5N1 and the use of educational programs (e.g., lectures, educational songs, interactive quiz, and use of leaflets and posters) and reported some increase in awareness of H5N1 and to seek early access to healthcare	Low	No	8/11 (rating by McMaster Health Forum)	2011	No	None identified
• Public health strategies	A systematic review of the costs and benefits of interventions aimed at major infectious disease	Low	No	4/9 (rating by McMaster)	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
○ Non-pharmaceutical public health strategies to prevent infection ▪ Using protective equipment (e.g., masks, gloves) ▪ Physical distancing ○ Non-pharmaceutical measures public health strategies to control the spread of infections ▪ Case and contact management ▪ Isolation and quarantine ○ Pharmaceutical measures used as part of public health strategies ▪ Vaccinations (in humans) ▪ Antiviral medications ○ Surveillance and reporting ● Priority populations ○ Groups at higher risk of exposure ▪ Working in healthcare settings and other contacts of cases (if human-to-human transmission starts)	threats (largely focusing on H1N1) revealed that vaccinations and school closures were the most commonly studied interventions, along with other physical distancing strategies ● A more standardized and comprehensive approach to economic evaluations of interventions. ● Current research focuses largely on high-income countries and pharmaceutical interventions.			Health Forum)			
● Public health strategies ○ Pharmaceutical measures used as part of public health strategies ▪ Vaccinations (in humans)	Adjuvanted H7N9 vaccines for humans were found to be immunogenic and safe in healthy individuals	High	No	7/11	2017	No	None identified
● Public health strategies ○ Pharmaceutical measures used as part of public health strategies ▪ Vaccinations (in animals)	While vaccines were efficacious to protect chickens from morbidity and mortality, virus shedding may be a biosecurity issue for future avian influenza outbreaks ● A meta-analysis was conducted on studies that focused on both inactivated and recombinant fowlpox virus expressing H5 vaccines to determine outcomes for H5N1 and H5N2 avian influenza viruses among chickens.	High	No	5/11	2010	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
- Public health strategies - Pharmaceutical measures used as part of public health strategies - Vaccinations (in animals)	Among chickens, recombinant herpesvirus of turkeys (rHVT) and inactivated replicating viral-vectored offer advantages to induce broader immunity as they are more tolerant of variation in the hemagglutinin 1 domain (HA1) A vaccine-induced antibody titres to the challenge virus of (VIAC) of ≥ 16 should be the minimum titre that may be sufficient for survival and reduction of virus shed in field studies.	High	No	5/11	25 May 2022	No	None identified

Appendix 4: Documents excluded at the final stages of reviewing

Document type	Hyperlinked title
Evidence syntheses	Antivirals for influenza in healthy adults: Systematic review
	Serological evidence of human infection with avian influenza a(h7n9) virus: A systematic review and meta-analysis
Literature reviews with no systematic searches	A brief introduction to avian influenza virus
	A brief history of bird flu
	A comprehensive review of highly pathogenic avian influenza (HPAI) H5N1: An imminent threat at doorstep
	A global perspective on H9N2 avian influenza virus
	A literature review of the use of environmental sampling in the surveillance of avian influenza viruses
	A review of avian influenza a virus associations in synanthropic birds
	A review of H5Nx avian influenza viruses
	A review of knowledge discovery process in control and mitigation of avian influenza
	A review on current trends in the treatment of human infection with H7N9-avian influenza A
	Adenoviral vectors as vaccines for emerging avian influenza viruses
	Alarming situation of emerging H5 and H7 avian influenza and effective control strategies
	An outbreak of highly pathogenic avian influenza (H7N7) in Australia and the potential for novel influenza a viruses to emerge
	An overview of avian influenza in the context of the Australian commercial poultry industry
	Avian influenza (H5N1) virus, epidemiology and its effects on backyard poultry in Indonesia: A review
	Avian influenza A (H7N9) virus: From low pathogenic to highly pathogenic
	Avian influenza A virus associations in wild, terrestrial mammals: A review of potential synanthropic vectors to poultry facilities
	Avian influenza in the greater Mekong subregion, 2003–2018
	Avian influenza in wild birds and poultry: Dissemination pathways, monitoring methods, and virus ecology
	Avian influenza overview June–September 2023
	Avian influenza revisited: Concerns and constraints
	Avian influenza viruses at the wild–domestic bird interface in Egypt
	Avian influenza viruses in humans: Lessons from past outbreaks
	Avian influenza: Strategies to manage an outbreak
	Backyard poultry: Exploring non-intensive production systems
	Control of avian influenza in China: Strategies and lessons
	Controlling avian influenza virus in Bangladesh: Challenges and recommendations
	Emerging and re-emerging infectious diseases in the WHO Eastern Mediterranean region, 2001-2018
	Emerging and re-emerging zoonotic viral diseases in Southeast Asia: One Health challenge
	Emerging diseases of avian wildlife

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

References

1. Chin KJ, Englesakis M, Lee Y, et al. Risk factors and protective measures for healthcare worker infection during highly infectious viral respiratory epidemics: A systematic review and meta-analysis. *Infection Control & Hospital Epidemiology* 2022; 43(5): 639-50.
2. 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.
3. Kellerborg K, Brouwer W, van Baal P. Costs and benefits of interventions aimed at major infectious disease threats: lessons from the literature. *Eur J Health Econ* 2020; 21(9): 1329-50.
4. Halton K, Sarna M, Barnett A, Leonardo L, Graves N. A systematic review of community-based interventions for emerging zoonotic infectious diseases in Southeast Asia. *JI Database System Rev Implement Rep* 2013; 11(2): 1-235.
5. Shi N, Huang J, Zhang X, et al. Interventions in Live Poultry Markets for the Control of Avian Influenza: A Systematic Review and Meta-analysis. *The Journal of Infectious Diseases* 2020; 221(4): 553-60.
6. Prieto-Lara E, Llanos-Méndez A. Safety and immunogenicity of prepandemic H5N1 influenza vaccines: a systematic review of the literature. *Vaccine* 2010; 28(26): 4328-34.
7. Zhang K, Wu X, Shi Y, Gou X, Huang J. Immunogenicity of H5N1 influenza vaccines in elderly adults: a systematic review and meta-analysis. *Hum Vaccin Immunother* 2021; 17(2): 475-84.
8. Keitel WA, Voronca DC, Atmar RL, et al. Effect of recent seasonal influenza vaccination on serum antibody responses to candidate pandemic influenza A/H5N1 vaccines: A meta-analysis. *Vaccine* 2019; 37(37): 5535-43.
9. Zheng D, Gao F, Zhao C, Ding Y, Cao Y, Yang T, Xu X and Chen Z, 2019. Comparative effectiveness of H7N9 vaccines in healthy individuals. *Human Vaccines & Immunotherapeutics* 2019; 15(1): 80-90.
10. Hsu SM, Chen THH, Wang CH. (2010). Efficacy of avian influenza vaccine in poultry: A meta-analysis. *Avian Diseases* 2010; 54(4): 1197-209.
11. Mo J, Spackman E, Swayne DE. 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. *Vaccine*. 2023;41(38): 5507-17.

Bhuiya A, Bain T, Demaio P, Wilson MG. Rapid evidence profile #64: Identifying features and impacts of public health strategies that can be used to prevent, reduce and/or mitigate avian influenza spillover to humans. Hamilton: McMaster Health Forum, 12 January 2024.

This rapid 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 rapid 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 Nujud Al-Jabouri, Samantha Cheng, Yao Maclean, Kunika Singh, and Tresha Sivanesanathan for conducting the AMSTAR appraisals.