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Dose Strategy for Vaccination Against Influenza A(H5N1) in Quebec

GUIDANCE AND RECOMMENDATIONS

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COMITÉ SUR L'IMMUNISATION DU QUÉBEC INTERIM SCIENTIFIC GUIDANCE

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AUTHORS

Comité sur l'immunisation du Québec

Caroline Quach-Thanh, Pediatric infectious diseases specialist and medical microbiologist
Centre hospitalier universitaire Sainte-Justine

Marilou Kiely, Assistant Professor
Department of Social and Preventative Medicine, Université Laval

Jesse Papenburg, Pediatric infectious diseases specialist and medical microbiologist
McGill University Health Centre, Montréal Children's Hospital

Isabelle Picard, Veterinarian and Zoonoses Coordinator
Ministère de l'Agriculture, des Pêcheries et de l'Alimentation du Québec

Ariane Massé, Biologist
Ministère de l'Environnement, de la Lutte contre les changements climatiques, de la Faune et des Parcs

Sophie Gagnon, Master's Student in Microbiology, infectious diseases, and Immunology at the Université de Montréal Faculty of Medicine

Nicholas Brousseau, Medical Officer
Philippe De Wals, Medical Officer
Direction des risques biologiques

Stéphane Caron, Medical Officer
Direction de la santé environnementale, au travail et de la toxicologie

UNDER THE COORDINATION OF

Laurence Pothier, Nursing Advisor
Brigitte Paquette, Scientific Unit Head
Direction des risques biologiques

CONTRIBUTORS

Carl A. Gagnon, Full Professor
Department of Pathology and Microbiology, Faculty of Veterinary Medicine, Université de Montréal

Lily Lessard, Director
Réseau de prévention des crises en santé (Précrisa)
Professor, Université du Québec à Rimouski

Kianoush Dehghani, Public Health Physician
Public Health Department of the Cree Board of Health and Social Services of James Bay

Marie-Josée Morin, Nurse Consultant in Immunization
Cree Board of Health and Social Services of James Bay

Marianne Picard-Masson, Medical Officer
Direction de la santé environnementale, au travail et de la toxicologie

Karl Forest-Bérard, Scientific Advisor
Secrétariat général, Affaires publiques, communications et transfert des connaissances

REVIEWERS

Alex Carignan, Infectious Disease specialist and medical microbiologist
Centre intégré universitaire de santé et de services sociaux de l'Estrie – Centre hospitalier universitaire de Sherbrooke

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Dr. Carignan reported participating in occasional training and consulting activities over the past three years for the following private companies whose products or activities fall within the field of vaccination: Pfizer, GSK, and Merck.

LAYOUT

Sarah Mei Lapierre, Administrative Officer
Direction du développement des individus et des communautés

Marie-France Richard, Administrative Officer
Direction des risques biologiques

ENGLISH TRANSLATION AND REVIEW

Mary Thaler
Emily Wilson

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Comité sur l'immunisation du Québec

ACTIVE MEMBERS

Julie Bestman-Smith
Centre hospitalier universitaire de Québec – Hôpital de l'Enfant Jésus

Nicholas Brousseau
Philippe De Wals
Rodica Gilca
Étienne Racine
Chantal Sauvageau
Direction des risques biologiques, Institut national de santé publique du Québec

Marilou Kiely
Department of Social and Preventative Medicine, Université Laval

Michaël Desjardins
Centre hospitalier de l'Université de Montréal

Jesse Papenburg
Montréal Children's Hospital, McGill University Health Centre

Caroline Quach-Thanh, Chair
Centre hospitalier universitaire Sainte-Justine

Louis Marois
Centre mère-enfant Soleil of CHU de Québec–Université Laval

LIAISON MEMBERS

Dominique Biron
Representative of the Fédération des médecins omnipraticiens du Québec

Ngoc Yen Giang Bui
Representative of the Comité consultatif québécois sur la santé des voyageurs

Hélène Gagné
Representative of the Table de concertation nationale en maladies infectieuses

Alain Jutras
Immunization Managers Representative

Benoît Morin
Representative of the Association québécoise des pharmaciens propriétaires

Annie Payette
Stéphanie Dion
Representatives of the Direction des opérations de santé publique
Santé Québec

Eveline Toth
Lina Perron
Representatives of the Direction de la vigie et des maladies infectieuses
Ministère de la Santé et des Services sociaux

EX OFFICIO MEMBERS

Brigitte Paquette
Patricia Hudson
Direction des risques biologiques, Institut national de santé publique du Québec

Maude Paquette
Representative of the Laboratoire de santé publique du Québec

FOREWORD

The Institut national de santé publique du Québec (INSPQ) is Quebec's public health expertise and reference centre. Its mission is to support the Ministre de la Santé et des Services sociaux, which is Quebec's Minister of Health and Social Services, in carrying out their public health responsibilities. The Institute's mission also includes, to the extent determined by its mandate from the Minister, supporting Santé Québec, the Nunavik Regional Board of Health and Social Services, the Cree Board of Health and Social Services of James Bay, and other institutions in the exercise of their public health mission.

The Guidance and Recommendations series brings together various scientific works under a single banner; these works highlight the best available scientific knowledge and add a contextual analysis that uses different criteria and deliberations to make recommendations.

This interim scientific guidance addresses the influenza H5N1 vaccination dosing strategy in Quebec in a context where there are a limited number of vaccine doses available in Canada.

It was developed at the request of the Direction de la vigie et des maladies infectieuses of the Ministère de la Santé et des Services sociaux (MSSS). This document is intended for the MSSS and for vaccination team managers and professionals in healthcare institutions.

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- In early 2025, the federal government purchased 500,000 doses of the Arepanrix™ vaccine against influenza A(H5N1) American wigeon clade 2.3.4.4b.
- In this context, the Ministère de la Santé et des Services sociaux (MSSS) asked the Comité sur l'immunisation du Québec (CIQ): **"What should be Quebec's vaccine strategy for A(H5N1) [...]?"**
- The main objectives of a potential vaccination program would be to prevent serious illness and infections in specific workers at high risk of exposure to highly pathogenic avian influenza A(H5N1).

CIQ recommendations

- Take a shared decision-making approach, rather than implementing a broad vaccination program targeting farm workers and the hunting population, by offering the vaccine to:
  - (i) personnel working with the live virus (culture/isolate) and at influenza A(H5N1) vaccine production sites;
  - (ii) veterinarians, technicians, and workers who perform necropsies on potentially infected animals, and diagnostic laboratory staff who are in contact with large numbers of potentially infected carcasses; and
  - (iii) workers who regularly participate in the management of cases on multiple farms, particularly during bird culling or the cleaning and disinfection of buildings; wildlife rehabilitation staff; and workers who regularly come into close or prolonged contact with potentially infected animals or samples, according to the risk assessment carried out by the Direction générale de la protection de la santé publique of the MSSS.
- Offer two doses with a two-month interval. The minimum 21-day interval could be considered in the event of human-to-human transmission.
- Evaluate this influenza A(H5N1) vaccination, particularly in terms of vaccine safety, immunogenicity, acceptance among different populations, vaccine coverage achieved, and logistical issues observed.

1 CONTEXT AND OBJECTIVES

Highly pathogenic avian influenza A(H5N1) is an emerging health threat, particularly for workers exposed to infected animals. Since 2003, nearly 1,000 human cases have been confirmed worldwide, with a high case fatality rate (around 50%). A(H5N1) viruses, clade 2.3.4.4b, were first detected in North America in migratory birds in late 2021, and have since been identified on all continents except Oceania. In North America, an increase in human cases was observed in 2024–2025, mainly among poultry and dairy workers in the United States. In several human cases, the infection was contracted without documented direct contact with infected animals (1,2). Fortunately, the fatality rate observed in 2024–2025 (around 2%) was lower than in the past.

In Canada, the first severe human case was reported in 2024, and recent mutations in the virus have been identified, raising concerns about a possible increase in the transmissibility and virulence of influenza A(H5N1) (3).

The clinical spectrum of human infection with influenza A(H5N1) is broad, ranging from mild symptoms (fever, conjunctivitis, cough) to severe illnesses such as acute pneumonia, encephalitis, and multi-organ failure, often resulting in death. The average incubation period is three to five days, but can be as long as 10 days.

In early 2025, the federal government purchased 500,000 doses of the Arepanrix™ vaccine against influenza A(H5N1). This vaccine, produced by GSK, was approved by Health Canada on February 18, 2025, for individuals six months of age and older. Sixty percent of the doses will be distributed to provinces and territories and 40% will be kept in a federal stockpile.

On February 19 of the same year, the Public Health Agency of Canada (PHAC) published the National Advisory Committee on Immunization (NACI)'s Preliminary guidance on human vaccination against avian influenza in a non-pandemic context as of December 2024. This NACI guidance "offers a preliminary framework to advise Canadian provinces and territories (PTs) on whether to use human vaccines against avian influenza (HVAI) in a non-pandemic context [...] to prevent human infection with avian influenza A(H5N1) viruses. Preventing transmission from animals to humans will help to prevent severe disease in humans and could also help limit opportunities for viral adaptations that could facilitate human-to-human transmission. In the event that PTs determine it is necessary to start offering HVAI, NACI has identified key populations to consider prioritizing for vaccination" (1).

In the context of reported outbreaks of avian influenza A(H5N1) in animals in Quebec, the Ministère de la Santé et des Services sociaux (MSSS) asked the Comité sur l'immunisation du Québec (CIQ) to answer the following question:

> **"What should be Quebec's strategy for vaccination against highly pathogenic avian influenza A(H5N1), given that Canada has a limited number of vaccine doses available?"**

Since highly pathogenic avian influenza A(H5N1) is found mainly in wild birds and in some poultry farms in Quebec, and since there is currently no human-to-human transmission, the main objectives of a potential vaccination program would be to prevent severe disease and infections in certain workers at high risk of exposure to highly pathogenic avian influenza A(H5N1).

The CIQ discussed the question put forward by the MSSS on March 14, 2025. Several experts were invited to participate. These experts were from the Ministère de l'Agriculture, des Pêcheries et de l'Alimentation du Québec (MAPAQ); the Ministère de l'Environnement, de la Lutte contre les changements climatiques, de la Faune et des Parcs (MELCCFP); the INSPQ's Direction de la santé environnementale, au travail et de la toxicologie; the Université de Montréal Faculty of Veterinary Medicine; the Interdisciplinary Chair on Health and Social Services for Rural Populations; and the Cree Board of Health and Social Services of James Bay. This scientific guidance summarizes the information discussed at the meeting and the recommendations approved by the CIQ members.

2 BURDEN OF DISEASE

2.1 In humans

Virological history

The highly pathogenic avian influenza (HPAI) A(H5N1) virus was first identified in humans in Hong Kong in 1997. It has since spread through various epidemic waves. Since 2003, 939 human cases have been confirmed worldwide, with a high case fatality rate (around 50%). In North America, an increase in human cases was observed in 2024–2025, mainly among poultry and dairy workers in the United States, some of whom contracted the infection without documented direct contact with infected animals (1–3).

The influenza A(H5N1) virus has evolved into distinct genetic clades, defined according to their mutations and circulation in various animal species. Clade 2.3.2.1c was mainly detected in Southeast Asia until 2018. Clade 2.3.4.4b is responsible for the global resurgence since 2021, affecting wild birds as well as wild and domestic mammals, especially dairy cattle and cats (4), and has altered the characteristics of infections in humans. Whereas historical cases of A(H5N1) were linked to direct exposure to infected poultry, more recent infections, particularly in the United States, have been linked to contact with infected dairy cows (58%), often via handling contaminated raw milk. However, exposure to poultry remains a significant source of infection (>35%) (1,3,5).

Recent evolution in North America (2024–2025)

In Canada, the first severe human case was reported in 2024, and recent mutations in the virus have been identified, raising concerns about a possible increase in its transmissibility and virulence. In the United States, as of March 4, 2025, 70 confirmed cases, including one death, have been recorded, the majority affecting farm workers (Table 1). The sources of exposure were: dairy cattle herds (41/70, 58.5%), poultry farms and culling operations (24/70, 34.3%), exposure from other animals, such as backyard flocks, wild birds, or other mammals (2/70, 2.9%), and unknown sources of exposure (3/70, 4.3%) (2). The two severe cases reported in North America were not associated with workplace exposure. The case of an adolescent in Canada had no identified source of exposure, and the death reported in Louisiana was linked to exposure to a combination of a non-commercial backyard flock and wild birds (6).

Of the 70 confirmed cases of influenza A(H5N1) in the United States, 38 (genotype B3.13) were recorded in California with detailed descriptions (7). Thirty-seven cases had been exposed to dairy cows. The median interval from the first A(H5) virus detection in cows to the first human case on a particular farm was seven days (range = -7 to 20 days). The majority of patients (76%) worked as milkers or cared for sick cows. Of these patients, the majority (78%) reported using personal protective equipment (PPE) at work, 25 (68%) wore gloves, 20 (54%) used eye protection (13 reported wearing goggles), 12 (32%) reported wearing boots, and six (16%) wore gowns. No patients specifically reported wearing a respirator (e.g., an N95 mask) as recommended; however, 12 (32%) reported wearing other face coverings or face masks. All

patients had mild symptoms. Frequently reported signs and symptoms included eye irritation or redness (97%), muscle aches (34%), and fever (29%). Respiratory symptoms were less commonly reported. All were offered oseltamivir; two declined (5%).

No cases were identified in household contacts of patients with occupational exposure. One confirmed case was detected through routine influenza surveillance in a previously healthy child who had no known contact with infected animals or humans and had not consumed unpasteurized dairy products. This patient, who had mild respiratory symptoms and otitis media but no conjunctivitis, was not hospitalized. Oseltamivir was prescribed when test results were positive for influenza A virus. Subtyping was positive for influenza A(H5) virus and serology testing revealed antibodies to influenza A(H5N1) (8). The patient's three household members also had respiratory symptoms: all specimens tested negative for influenza A(H5) virus. Specimens from the patient and two household members tested positive for adenovirus and rhinovirus.

Until recently, all detections of A(H5N1) in dairy cattle herds belonged to genotype B3.13, thought to be the result of a single introduction from wild birds in late 2023 or early 2024, followed by spread between cows and herds. In early 2025, a further spread of A(H5N1) to dairy cows involving genotype D1.1 was detected. A commercial poultry worker in Ohio (February 2025) involved in the culling of sick poultry was infected with genotype D1.3 of clade 2.3.4.4b. Since the fall of 2024, genotype D1.1 has represented the predominant genotype in North America in birds, infected wild mammals, and poultry farms (9).

Table 1 Human cases of influenza A(H5N1) recorded in North America since March 2024

Period	Number of confirmed human cases	Exposure	Main symptoms	Deaths
March 2024 – March 2025 (U.S.)	70 (cases) (2) (2 hospitalizations, 1 death)	Contact with infected cattle (41 cases), poultry (24 cases), other (2 cases), unknown exposure (3 cases)	Conjunctivitis (93%), fever (49%), respiratory symptoms (36%)	1
2024 (Canada)	1 severe case (intensive care hospitalization)	Unknown exposure	Acute respiratory distress	0

Factors influencing disease severity in 2024–2025

In 2024–2025, human infections with the A(H5N1) virus showed an atypical pattern compared with previous decades. Whereas historical cases were highly lethal (around 50%), recent infections, particularly in the United States, have been less severe, with mostly benign and localized manifestations. Several factors could explain this apparent decline in clinical significance. One key factor is the nature of the 2.3.4.4b clade currently predominant in North America. This clade, while still capable of infecting humans, appears to have mutations that reduce its affinity for the lower respiratory tract, where it could cause severe pneumonia. Unlike previous A(H5N1) viruses, it has shown an affinity for the conjunctiva and upper respiratory tract, which would explain why 93% of cases identified in the United States suffered from conjunctivitis rather than severe pulmonary infections (10,11).

The majority of cases (1,5) in 2024 and 2025 appear to have been acquired through contact with mastitis-affected cows, or by ingesting or having physical contact with raw milk from infected cows. This mode of transmission could potentially be associated with a reduced risk of lower respiratory complications, a hypothesis supported by the fact that the historical cases and severe cases of 2024–2025 were more likely to have been transmitted by inhalation of particles excreted by infected poultry. Most of the less severe recent human cases were caused by genotype B3.13, whereas the more severe human cases of A(H5N1) recorded in 2024–2025 were of genotype D1.1. Moreover, early administration of antivirals, particularly oseltamivir, may have played a role in limiting infection progression. In the United States, 87% of patients received this treatment soon after the onset of initial symptoms (11).

In addition, recent surveillance efforts, enabling more rapid detection of asymptomatic or mildly symptomatic cases, may have provided a more realistic picture of the clinical manifestations of highly pathogenic avian influenza. Earlier data, which reported a case fatality rate of 50%, may have been affected by a biased denominator as only the more severe cases were likely detected. The majority of cases detected in North America occurred in healthy workers; the severity of the disease in the general population remains uncertain. Finally, pre-existing immunity could explain

the lower severity of symptoms, a phenomenon that has been described in ferrets. Ferrets exposed to influenza A(H1N1)pdm09 developed cross-immunity to certain components of the A(H5N1) virus, resulting in lower viral replication compared to ferrets without cross-protection (12). Another recent study also demonstrated that ferrets with antibodies from previous infection with the seasonal influenza A(H1N1)pdm09 (A/California/7/2009) virus who were subsequently infected with avian influenza A(H5N1) virus were less severely ill and less likely to transmit the virus to other ferrets in the same enclosure than ferrets with no pre-existing immunity to the influenza virus (13).

To date, there are insufficient data to draw a definitive conclusion as to whether the lower severity of infection is due to the specific clade and genotype involved, the mode of transmission, more comprehensive case surveillance, pre-existing immunity, or early treatment of cases with antiviral drugs. Nevertheless, although the recent evolution of A(H5N1) seems to be associated with reduced clinical severity, the severity of the disease remains uncertain, and the virus continues to evolve. The emergence of certain mutations of concern, combined with the virus's spread to new hosts, warrants continued vigilance, particularly in terms of farm biosecurity and animal and human virological surveillance (1). Resistance to neuraminidase inhibitors (i.e., oseltamivir, peramivir, zanamivir) remains very rare in clade 2.3.4.4b A(H5N1) viruses (14,15).

Seroprevalence data presented by Dr. Danuta Skowronski (oral presentation, CIQ, March 14, 2025) on sera collected from August 18 to 28, 2024, in diagnostic laboratories located outside of hospitals (LifeLabs), stratified by age group, demonstrated that cross-immunity between seasonal influenza and influenza A(H5N1) exists in the population, notably through anti-neuraminidase (N1) activity. The cohorts of people with the lowest cross-immunity to influenza A(H5N1) were born between 1957 and 1976, a period when H2N2 and H3N2 were predominantly circulating. Since the first influenza virus encountered by these cohorts was subtype N2, their immune response is lower when exposed to subtype N1. The same is true for children born between 2014 and 2024, after the A(H1N1)pdm09 pandemic, because although the pandemic virus was still circulating, it was co-circulating with the A(H3N2) virus, and exposure to the A(H1N1) virus was lower than in the peripandemic years (2009).

Public health implications in Quebec

The current influenza A(H5N1) outbreak in the United States and Canada is unprecedented, as the virus's spread in dairy cattle farms in the United States has altered the clinical characteristics of human infections. Despite an overall low risk to the general population, certain farm workers, wildlife workers (rehabilitation), veterinarians, and laboratory personnel remain at high risk, warranting increased surveillance and consideration of a targeted vaccination strategy. NACI emphasizes that the decision to implement a vaccination program for influenza A(H5N1) depends on how circulating strains evolve and their impact on human health. In Quebec, enhancing surveillance (16) by systematically subtyping identified influenza viruses and implementing a serological surveillance program for workers in affected sectors, reinforcing biosafety and personal protective measures for workers in contact with infected animals, and assessing targeted vaccination for certain at-risk groups could help limit the impact of this emerging threat.

2.2 In animals

Since the HPAI A(H5N1) clade 2.3.4.4b virus was identified in birds in Quebec in April 2022, it has spread mainly via wild bird migration. It has affected several species of wild birds and mammals, as well as numerous poultry farms. Other A(H5Nx) viruses are also emerging internationally, some of which have been identified in Quebec (Table 2).

Table 2 Animals positive for H5 avian influenza in Quebec from January 1, 2022, to February 5, 2025

Health regions	Wild animals		Poultry farms	
	A(H5N1)	A(H5)	A(H5N1)	A(H5N2)
Abitibi-Témiscamingue	0		0	
Bas-Saint-Laurent	74	1 H5*	0	
Capitale-Nationale	22		5	
Chaudière-Appalaches	25	1 H5N5	1	1
Côte-Nord	34		0	
Estrie	55		18	
Gaspésie–Îles-de-la-Madeleine	36		0	
Terres-Cries-de-la-Baie-James	0		0	
Lanaudière	15		1	
Laurentides	17		1	
Mauricie and Centre-du-Québec	40	1 H5*	5	
Montérégie	100	11 H5*	23**	3
Montréal	6		0	
Nunavik	2		0	
Outaouais	6		1	
Saguenay–Lac-Saint-Jean	4		0	
Total	**436**	**14**	**55**	**4**

* Subtyping and confirmation underway

** 5 cases are reinfections at previously affected farms

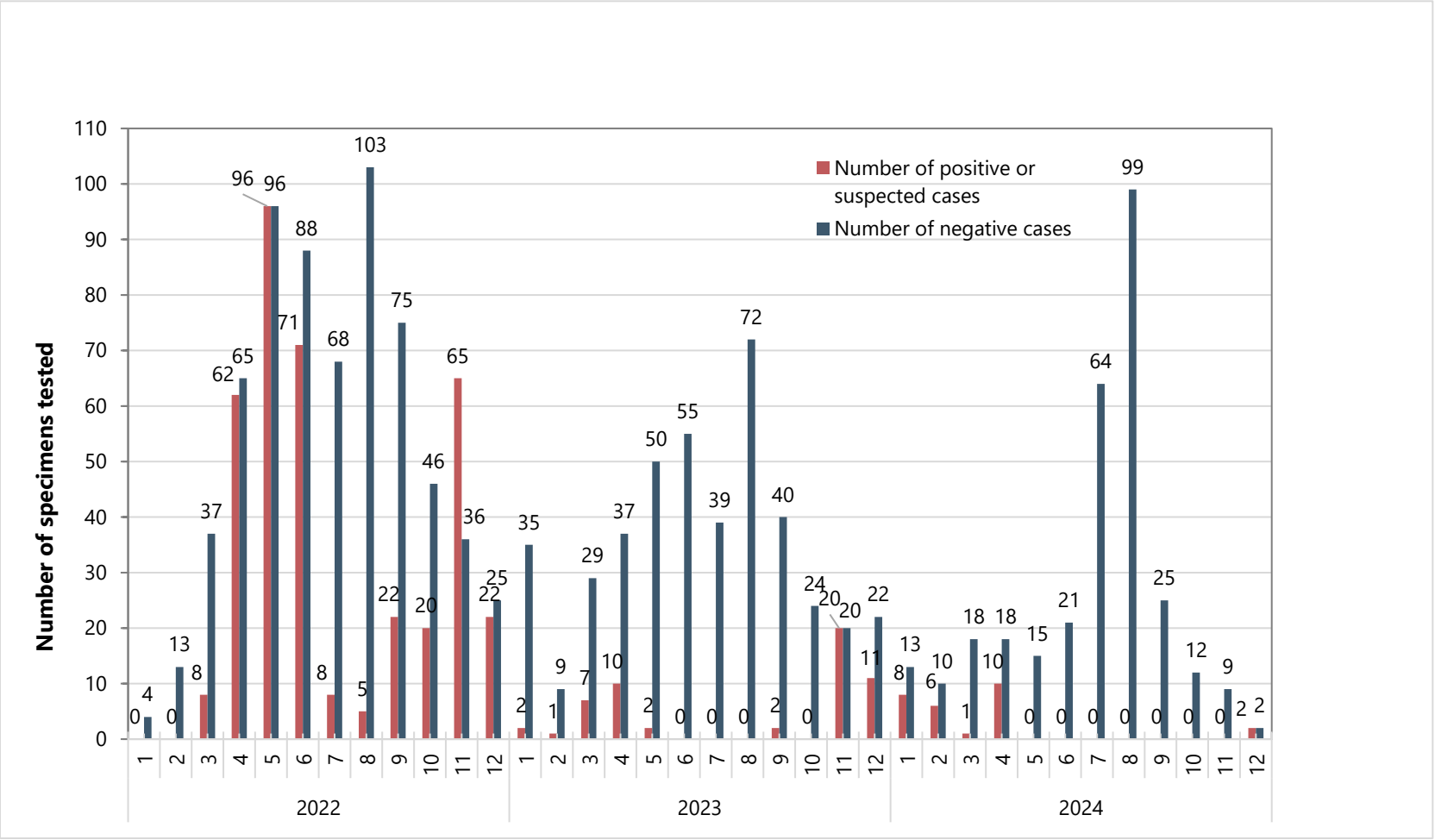
Note: Wild birds often show no signs of the disease, and death rates are generally low. Ducks, geese, gulls, and other waterfowl can maintain the virus in their populations and spread it undetected. Some species, however, may be more susceptible and experience greater mortality rates. In Quebec, increased mortality has been observed in gannets, common eiders, great black-backed gulls, turkey vultures, and birds of prey (http://www.quebec.ca/avianinfluenza).

Sources: Centre québécois sur la santé des animaux sauvages (CQSAS), Ministère de l'Environnement, de la Lutte contre les changements climatiques, de la Faune et des Parcs (MELCCFP), Ministère de l'Agriculture, des Pêcheries et de l'Alimentation (MAPAQ)

Cases of avian influenza A(H5N1) in wild birds are often identified near densely populated areas (e.g., Montérégie), as birds collected for surveillance purposes are reported by citizens. It should be noted that the number of specimens from the health regions of Nunavik and Terres-Cries-de-la-Baie-James is limited. Mass mortalities were observed in the Bas-Saint-Laurent, Gaspésie–Îles-de-la-Madeleine, and Montérégie (Saint-Jean-sur-Richelieu) health regions in 2022. As only the first few specimens are analyzed during mass mortalities, the data in Table 2 reflect only a small part of the total burden of infection.

In Quebec, cases of avian influenza A(H5N1) occur mainly during the wild bird migration periods in spring and fall, when birds concentrate in large numbers along the St. Lawrence Valley (Figure 1). Summer and winter are less favourable to the virus's survival in the environment and to its spread (17). Wild birds contaminate their environment according to several factors, including their level of immunity. The majority of cases occurred when the virus was introduced in Quebec in 2022. The presence of the year's juvenile birds, naive to the virus during the fall migration, could explain why peaks in cases may be slightly higher in the fall compared to the spring. The presence of immunity to the virus is likely to reduce viral replication and disease severity in birds, as demonstrated in experiments with ferrets (12,13). The more carcasses of infected birds and droppings that contain the virus contaminate the environment, the greater the infection pressure, leading to cases in wild mammals and poultry farms. Of the 59 cases of avian influenza A(H5Nx) on poultry farms, 24 occurred in spring and 19 in fall.

Figure 1 **Number of wild animal specimens found dead or sick and tested as part of avian influenza surveillance in Quebec from 2022 to 2024 (by month)**



Sources: Centre québécois sur la santé des animaux sauvages (CQSAS), Ministère de l'Environnement, de la Lutte contre les changements climatiques, de la Faune et des Parcs (MELCCFP), Ministère de l'Agriculture, des Pêcheries et de l'Alimentation (MAPAQ)

In Canada, only the poultry sector is currently affected. In a poultry flock, the mortality rate quickly reaches almost 100%. Each case on a poultry farm prompts an intervention that includes the immediate culling of the affected flock. In Canada, over 14 million domestic birds have been destroyed (data from February 2025 [18]) in an attempt to control the spread of HPAI.

Active surveillance has been in place in the dairy cattle sector since spring 2024. Efforts have been made to raise awareness among farmers and veterinarians to increase vigilance. To date, control measures at the United States border and biosecurity have prevented the virus's introduction into this sector in Canada. Cases occurring on dairy farms would be controlled by several weeks of quarantine, until the virus is eliminated from the herd. The disease in cattle is associated with a low mortality rate, with deaths due to the culling of some cows that remain less productive after infection. On positive farms, milk from cows without any sign of disease continues to be collected. It is then transported to a processing plant, where it undergoes mandatory pasteurization to eliminate any virus it may contain. This process involves a risk of exposure over a long period for workers deemed essential to the farm, as well as for the workers handling raw milk (breeders; farm workers responsible for milking, feeding, and cleaning/disinfection; veterinarians; inseminators; milk collectors and testers; milk transporters and processors).

In Canada, risks to consumers are currently managed through herd health surveillance, slaughter plant surveillance, and regulations surrounding the marketing of animal products. There is no evidence that the virus can be transmitted to humans through the consumption of poultry, game, eggs, or other foods that are properly prepared, pasteurized, or cooked.

3 CHARACTERISTICS OF THE AREPANRIX™ H5N1 (A/AMERICAN WIGEON CLADE 2.3.4.4b) VACCINE

The characteristics of the Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b) vaccine, considered in this guidance, are described in **Table 3**. The vaccine has an 18-month shelf-life (19) from the date of production, with an extension that will be assessed as and when required.

The Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b) vaccine is an update of the Arepanrix™ H5N1 (A/Indonesia de clade 2.1.3.2) vaccine authorized in Canada in 2013 (20). It contains an AS03 adjuvant and is administered as a two-dose series, with an interval of 21 days or more. It was modified to improve the immune response against the avian influenza A(H5N1) clade 2.3.4.4b strain currently circulating in animals. In ferrets, the H5N1 (A/American wigeon clade 2.3.4.4b) strain induced a robust response against the avian influenza A(H5N1) strain currently in circulation (21).

Table 3 Characteristics of the Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b) vaccine

Type of vaccine	• Inactivated split-virion, egg-based vaccine
Authorized ages for use	• Adults and children six months of age and above
Authorized dose and schedule	• Adults 18 years of age and above: two 0.5 mL doses of Arepanrix™ H5N1 (A/American wigeon) • Children and adolescents 6 months to 17 years: two 0.25 mL doses of Arepanrix™ H5N1 (A/American wigeon) • Interval: at least three weeks (21 days) between doses
Potential allergens	• Trace egg protein, including ovalbumin (≤0.083 mcg per dose) • Polysorbate 80 • Thimerosal
Adjuvant and preservatives	• AS03: α-tocopherol, squalene, and polysorbate 80 in an oil-in-water emulsion
Contraindications	• History of an anaphylactic reaction (i.e., life-threatening) to any of the constituents of the vaccine. The CIQ does not consider that egg anaphylaxis is a contraindication.
Storage	• 2°C to 8°C
Handling	• Use the vaccine within 24 hours of mixing the adjuvant with the antigen. The mixed vaccine can either be stored in a refrigerator (2°C to 8°C) or at room temperature (up to 30°C). If the mixed vaccine is stored in a refrigerator, it should be allowed to reach room temperature (for a minimum of 15 minutes) before each withdrawal.
Reconstitution	• The vaccine is reconstituted by withdrawing the entire content of the vial containing the adjuvant with a 5 mL syringe and by adding it to the vial containing the antigen. The vaccine should be mixed thoroughly by inversion. The mixed final product for administration is an emulsion containing 10 doses (0.5 mL each).
Route of administration	• Intramuscular injection
Syringe and needle selection	• 1 mL syringe for injection, needle gauge not larger than 23-G

Immunogenicity (Arepanrix™ H5N1 A/Indonesia clade 2.1.3.2)

There is no available data on the immunogenicity or efficacy of Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b). Health Canada's authorization is based on indirect data from a H5N1 vaccine containing the A/Indonesia clade 2.1.3.2 strain. This is standard practice for strain changes in seasonal influenza vaccines: clinical trials are not required to justify the authorization of a new seasonal influenza vaccine (22) with an updated strain.

The immunogenicity of Arepanrix™ H5N1 (A/Indonesia clade 2.1.3.2) was assessed in six randomized trials. The vaccine was produced in Quebec (Q-Pan vaccine). Three supportive studies of a vaccine produced in Germany using the A/Vietnam strain (D-Pan vaccine) were reviewed as part of the authorization application to Health Canada (23).

Study Q-Pan-002 was the pivotal study for immunogenicity and safety that served as the basis for authorization. It was a phase III, randomized clinical trial. Two 0.5 mL doses of H5N1 (A/Indonesia clade 2.1.3.2) vaccine with AS03 were administered to adults, 21 days apart. A total of 4,561 individuals participated in the study and were vaccinated, with 3,422 in the Q-Pan group and 1,139 in the placebo group (23). The seroprotection rates (percentage of subjects with a reciprocal hemagglutination inhibition titer of ≥1:40) against the homologous strain ranges from 76.8% (persons aged 60 and over) to 91.0% (persons aged 18–60), 21 days following the second dose, which exceeded the authorization criteria typically used for influenza vaccines (≥70 %). The seroprotection rates were 62% and 63.5% six months after the first vaccination. It is difficult to draw conclusions about the durability of the immune response from these data.

The response to the Q-Pan vaccine against heterologous strains (A/Vietnam/1194/2004, A/turkey/Turkey/1/2005, and A/Anhui/01/2005) was far less robust. Immune responses were stronger against heterologous strains belonging to the same clade as the vaccine strain than against those of different clades. It is difficult to know how well the Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b) vaccine would protect against heterologous strains (24). Unpublished data presented to NACI suggest that the Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b) vaccine induces good humoral immunity against the A(H5N1) strain that infected an adolescent in B.C.

Three studies assessed the immune response against the homologous strain after a single dose (on day 21). Most results regarding antibody titers did not meet the immunogenicity criteria used for authorization (24–27).

Finally, one study using the D-Pan vaccine included children three to nine years of age. Twenty-one days after the administration of two half-doses (0.25 mL), the seroprotection rates against the homologous strain were nearly 100%, and after six months, seroprotection remained above 70%.

The immunogenicity of Arepanrix™ H5N1 was not tested for different intervals between doses, and to our knowledge, there is no such available data for other influenza vaccines. Nonetheless, experience with other viral and bacterial vaccines indicates that longer intervals between the first two doses, of up to six months, are associated with a better immune response compared to a shorter interval of 21 days (28).

Safety (Arepanrix™ H5N1 A/Indonesia clade 2.1.3.2)

Clinical studies of Arepanrix™ (A/Indonesia clade 2.1.3.2) have demonstrated that the vaccine has an acceptable safety profile. Reported local adverse events included pain, redness, swelling, induration, and ecchymosis. General adverse events included fever, fatigue, headache, myalgia, shivering, arthralgia, and increased sweating (23). As the use of Arepanrix™ H5N1 (A/Indonesia clade 2.1.3.2) was limited to clinical trials, there is no available phase IV (post-marketing) data.

During the influenza A(H1N1) pandemic in 2009, adjuvanted vaccines Arepanrix™ H1N1pdm09 and Pandemrix™ H1N1pdm09, produced by GSK, were used in Canada and some other countries. A different strain was included in the Arepanrix™, but the vaccine was produced in the same facilities as the H5N1 vaccine discussed in this guidance. One study in Quebec and one study in Germany found a slightly increased risk of Guillain-Barré syndrome (GBS) following the use of these vaccines (around two cases per million doses). A similar risk was also identified in other countries with other vaccines, including in the United States (29). An increased risk of GBS after influenza vaccination was also identified in other contexts, notably during a swine flu pandemic threat in 1976 (29), when 10 cases of GBS were identified per million doses administered.

A safety signal was detected for narcolepsy with Pandemrix™ H1N1pdm09. The vaccine was associated with an increase in narcolepsy cases in children and adolescents in Europe, with relative risks in people 5 to 19 years of age of 7.5 (Sweden) and 6.4 (Finland), compared to pre-pandemic rates (30). In Quebec, a lower possible risk of around one case per million doses was identified with Arepanrix™, but confounding factors could also explain this association (e.g., infection with the A/H1N1pdm09 virus itself). No association between vaccination with Arepanrix H1N1pdm09 and narcolepsy was identified in Ontario (31). It is impossible to determine from these data whether there will be an association between the Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b) vaccine and an increased risk of narcolepsy or GBS.

Finally, in Quebec, surveillance of the use of Arepanrix™ H1N1pdm09 revealed a relatively high rate of anaphylaxis after vaccination. Thirteen cases per million doses administered were reported, which is higher than rates described for seasonal influenza vaccination (32). It should be noted, however, that a review and analysis of anaphylaxis cases reported with Arepanrix and Pandemrix led to the diagnosis being ruled out in 45% of cases, reducing the rate to between 0.8 and 1.5 cases per million doses administered. The case review revealed that many anaphylaxis diagnoses were actually cases of vasovagal shock, isolated urticaria without other symptoms, hyperventilation-related symptoms (numbness of limbs or mental fog/confusion), or hypotension/fainting linked to needle or injection phobia.

Other available vaccines

In addition to Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b), other vaccines have been developed to protect against A(H5N1) clade 2.3.4.4b. In Finland, an adjuvanted H5N8 (A/Astrakhan clade 2.3.4.4b) vaccine from CSL Seqirus was administered to some workers on a two-dose schedule. Upon the vaccination of 39 people, the seroprotection rates were 84% (microneutralization) and 97% (hemagglutinin inhibition) (33). In a subgroup of workers previously vaccinated with an H5N1 vaccine between 2009 and 2018, a single dose of vaccine elicited seroprotective titers, indicative of an anamnestic response. The authors concluded that the vaccine is expected to confer adequate protection against the currently circulating avian influenza virus of clade 2.3.4.4b.

Currently only Finland has used a H5Nx vaccine to protect workers against avian influenza (H5N8 A/Astrakhan clade 2.3.4.4b vaccine). Other jurisdictions have ordered updated clade 2.3.4.4b vaccines, but have not yet used them. For instance, England signed a 5 million-dose contract to be used in the event that avian influenza of clade 2.3.4.4b start spreading between humans, and only until a pandemic vaccine is produced (34).

4 ACCEPTANCE AND FEASIBILITY

4.1 Acceptance in the agriculture, poultry, and veterinary sectors

At present, no data are available on the acceptance of avian influenza vaccines in a non-pandemic context in Quebec and Canada. A few studies have reported a low vaccine uptake (VU) for seasonal influenza vaccination in populations that could be targeted by the avian influenza vaccine. Data from England, dating back more than 15 years, suggested VUs of poultry industry workers ranging from 7% to 29% in a questionnaire study completed by consultants in public health from Primary Care Trusts operating at five clinics, and a VU of 32% in a study evaluating the implementation of a vaccination program in a specific county (35,36). In a recent survey of poultry workers and people in direct contact with birds in England, VC against seasonal influenza was 32% among those reporting exposure to the avian influenza virus (37). Lower VUs were also noted for children and adults living in rural areas of Canada, versus those living in urban areas, with the former potentially being a population at greater risk of exposure to the avian influenza virus (38,39).

In June 2024, Finland rolled out an avian influenza vaccination program targeting individuals at increased risk of contracting avian influenza due to their work or other circumstances. These individuals included workers at fur and poultry farms, veterinarians, and lab technicians. In late January 2025, 516 targeted individuals received at least one vaccine dose, and 444 received the two recommended doses of the vaccination series for an estimated vaccine coverage of around 5%. One possible reason for this low VU is that the vaccination program was launched in June 2024, several months after the last A(H5N1) virus was detected in a wild bird (January 2024).

4.2 Feasibility

Overview of Quebec's key populations targeted by NACI

An approximate overview of the number of facilities and workers in some of the key populations identified by NACI in its preliminary guidelines was produced. It is presented in Tables 4 and 5 in the appendix and details the number of individuals, when available, who belong to the groups examined. The information presented comes from the Ministère de l'Agriculture, des Pêcheries et de l'Alimentation du Québec (MAPAQ); the Ministère de l'Environnement, de la Lutte contre les changements climatiques, de la Faune et des Parcs (MELCCFP); the *Système d'information en santé au travail* (SISAT), which is Quebec's occupational health information system; and relevant government and professional association websites. As data on farm residents was not available, only information on the number of workers was obtained. There are several limitations to the SISAT data: 1) the data come from the files of the Commission des normes, de l'équité, de la santé et de la sécurité du travail (CNESST) and may be several years old, reflect an estimate, and have not been validated by the Réseau de santé publique en santé au travail (RSPSAT); 2) self-employed workers, family farms, and farms without workers are not included; 3) farm subcontractors are not included; and 4) some temporary workers may be excluded.

Implementation of preventive measures against HPAI

Since July 2022, recommendations (40) have been in effect for: 1) workers in contact with birds or other wild animals (41), and 2) poultry farmers, regarding the preventive measures to apply in the presence of HPAI. Information from the MAPAQ and the Quebec Poultry Disease Control Team (EQCMA) indicates that poultry farms have experienced difficulties in implementing certain preventive measures, particularly in relation to respiratory protection devices, in terms of both accessibility and proper use. As the agricultural sector is not one of the sectors of activity covered by regulation, it has not been included in regular interventions by the occupational health teams of Quebec's public health departments.

It should be noted that, at least in Terres-Cries-de-la-Baie-James, public health authorities encourage Cree hunters and their families to use safe hunting practices, including the use of certain personal protective equipment when handling, plucking, and hunting wild birds. However, the application of these preventive measures is probably insufficient. Furthermore, birds are generally plucked and prepared in poorly ventilated indoor spaces, and in the presence of several family members, including children, who take part in the operation.

Workplace vaccination programs

In the early 2000s, the occupational health teams of Quebec's public health departments participated in two integrated intervention programs addressing biological risks. Phase 1 targeted police officers, firefighters, and penitentiary guards for blood-borne virus protection, and Phase 2 targeted sewage workers because of their exposure to wastewater. These programs provided information, support, and prevention measures, including vaccination against hepatitis B in Phase 1 and against hepatitis A in Phase 2. These initiatives took place over several years of planning and intervention involving the occupational health network, the CNESST, and the concerned workplaces. Vaccination campaigns were held at the workplaces with informed consent; the participation rate was high, but it is important to note that the targeted workplaces were unionized and highly involved in organizing the activities.

5 UNKNOWNS AND RESEARCH QUESTIONS

There are currently no vaccine efficacy data for Arepanrix™ A(H5N1). However, the immunogenicity data for this vaccine with a different strain are reassuring. It is therefore expected that the immunogenicity of the updated vaccine will be similar. The vaccine safety will need to be monitored in larger cohorts, particularly given that cases of narcolepsy and Guillain-Barré syndrome were reported in some jurisdictions following the use of Arepanrix and Pandemrix A(H1N1)pdm09 in 2009.

It is impossible to predict whether the cross-protection reported against viruses of the same clade (2.3.4.4b) will persist if the HPAI virus mutates sufficiently to allow transmission between humans. It is also difficult to predict the potential impact of using a vaccine containing an avian virus on immune imprinting.

6 ETHICS AND EQUITY

Given the unknowns and the objective of the program, the principle of **beneficence** supports prioritizing protection for people most at risk of exposure to the HPAI virus, particularly those who would be at high risk but are not covered by an occupational health program with personal protective equipment and an appropriate infrastructure, or those who handle live HPAI viruses in the course of their work (e.g., in research settings). On the other hand, the principle of **nonmaleficence** is at odds with the aim of beneficence. Non-maleficence refers to the principle that those targeted by vaccination not be unduly exposed to risks that could otherwise be avoided. It is therefore important to be able to assess the balance between these two principles.

What is known and what is unknown must be presented to people in a fully **transparent** manner and, in a pre-pandemic context, the decision on whether to be vaccinated should be discussed with the target groups to respect their **autonomy** in the decision-making process (shared decision-making). Some people at high risk of exposure may prefer to be vaccinated, knowing the possible risks.

From an **equity** standpoint, since the vaccine is not available on the private market, high-risk individuals can only be vaccinated through a public health initiative. Scientific literacy is also likely to influence individuals' final decisions on whether to accept vaccination.

7 LEGAL ISSUES RELATING TO OCCUPATIONAL HEALTH

The Act respecting occupational health and safety (42) sets out the legal provisions governing prevention in Quebec workplaces, and aims for the elimination, at the source, of dangers to the health, safety, and physical and mental well-being of workers. Every employer must take the necessary measures to protect the health and ensure the safety and physical and mental well-being of the worker (CQLR c S-2.1, s 51), and must, in particular:

- use methods and techniques intended for the identification, control, and elimination of risks to the safety or health of the worker;
- give the worker adequate information as to the risks associated with their work and provide them with the appropriate training, assistance, or supervision to ensure that they possess the skill and knowledge required to safely perform the work assigned to them; and
- provide the worker with all the individual protective means and equipment selected by the health and safety committee in accordance with paragraph 4 of section 78 or, as the case may be, the individual or collective protective means and equipment determined by regulation – free of charge – and require that the worker use these devices and equipment in the course of work.

The worker must also take the necessary measures to ensure their own health, safety, or physical or mental well-being (CQLR c S-2.1, s 49). The Act does not make specific reference to vaccination.

The Regulation respecting occupational health and safety (43) makes only one mention of vaccination, concerning free vaccinations for divers:

- Any diver working in a contaminated environment must be provided free of charge with vaccines against polio, tetanus, hepatitis A, and any other vaccine prescribed by a diving physician (section 312.72).

The Quebec Immunization Protocol (*Protocole d'immunisation du Québec* [PIQ]) includes vaccine recommendations for certain workers.

8 ALIGNMENT WITH OTHER PROGRAMS

At the time of writing, no province had issued recommendations on vaccination against H5N1, although various provincial committees planned to examine the issue. The Advisory Committee on Immunization Practices (ACIP) in the United States has not yet taken a position; their meeting, originally scheduled for late February 2025, was postponed. Finally, in the United Kingdom (44), the British government has signed a contract for the purchase of over five million doses of H5 human influenza vaccine to strengthen the country's resilience in the event of an H5 influenza pandemic. The influenza A(H5N8) vaccine, based on the current H5 avian influenza virus, will be manufactured by the British company CSL Seqirus UK Limited. No pre-pandemic vaccination recommendations have been made to date.

9 RISK ASSESSMENT

At present, the risk of influenza A(H5N1) clade 2.3.4.4b infection in the general population is considered very low to low (45–47): cases of infection in humans are rare and are transmitted by direct or indirect contact with infected animals. No human-to-human transmission of influenza A(H5N1) of clade 2.3.4.4b has been reported.

To date, 91 cases of human infection with clade 2.3.4.4b have been reported worldwide, over two-thirds of which occurred in the United States (2). Worldwide, more than half of cases are associated with contact with infected birds, mainly on commercial farms; the other reported human cases have resulted from contact with infected dairy cows or an unknown source. Eight severe cases have been reported worldwide, all following contact with infected birds (mainly backyard flocks) or with an unknown source, including two deaths (China and the United States). In Canada, there has currently only been one human case, a teenager in British Columbia, of which the source remains unknown; the individual experienced severe illness but survived.

Currently, reports of HPAI-infected wildlife are steadily declining, and no influenza A(H5N1) virus has been detected on Canadian dairy farms (48). Since 2022, there have been 59 outbreaks of H5N1 influenza in poultry farms (chickens, ducks, and turkeys) in Quebec (49), including seven in 2024 and one in 2025.

According to the Public Health Agency of Canada (PHAC) (46), the risk of infection with a clade 2.3.4.4b virus remains very low to low for people who have contact at less than two metres or prolonged contact with non-infected animals (wild birds, poultry, and mammals). This risk is also low to very low for people who have had contact with infected biological materials or fluids (feces, blood, secretions, tissues) from the animals mentioned or contact with an environment heavily contaminated by infected animals. However, the risk of infection is considered moderate when an individual has contact at less than two metres or prolonged contact with infected animals, and contact with an environment highly contaminated by infected animals.

Currently in Quebec, the individuals who may be considered at higher risk of infection by influenza A(H5N1) clade 2.3.4. 4b are workers who have close or prolonged and repeated contact (for example, in several facilities experiencing outbreaks) with infected live or dead poultry on poultry farms (some veterinarians working for the Canadian Food Inspection Agency [under federal jurisdiction], workers involved in poultry culling and in cleaning and disinfection, and laboratory workers who manipulate, handle, or culture the live avian influenza A[H5N1] virus). The risk assessment is based on the epidemiological situation and may change as the situation evolves.

10 CONCLUSIONS AND RECOMMENDATIONS

In the current epidemiological context in North America, Canada, and Quebec, and given the limited availability of the adjuvanted (AS03) Arepanrix™ H5N1 vaccine, the objective of an H5N1 vaccination program should be to prevent infections and illnesses caused by the virus among the most exposed workers, with a particular focus on preventing severe disease. A secondary objective would then be to reduce the risk of secondary cases occurring in close contacts of infected workers.

As with all influenza vaccines, Arepanrix™ H5N1 is likely to be more effective in reducing the severity of infections than in preventing infection altogether. It is also likely that an infected person with no or few symptoms will be less contagious than a highly symptomatic person. Workers who could be targeted are those with a high likelihood of frequent and intense exposure to potentially infected wild or domestic birds, or to potentially infected animal samples or products.

If infected cattle are reported in Canada, vaccination could be extended to certain workers in the Quebec's cattle industry. Other objectives like preventing reassortment or mutations that could generate a pandemic strain, protecting certain segments of the general population, or delaying the spread of a pandemic in Quebec, are considered unrealistic at this time, based on the assessment described in this guidance.

The recommendations that follow consider:

(i) the current burden of disease in both animals and humans;

(ii) that the few serious infections have mainly occurred in people who were not farm workers, but part of the general population;

(iii) the duration of protection conferred by the Arepanrix™ H5N1 vaccine (based on immunological data for the H5N1/A/Indonesia vaccine);

(iv) the risk of virus mutation, which could result in the loss of cross-protection conferred by the vaccine;

(v) the unknowns regarding serious adverse clinical events following vaccination;

(vi) the unknown impact of vaccination on worker behaviour, the availability of non-pharmacological protective measures, and the risk of infection by avian influenza other than A(H5N1) clade 2.3.4.b; and

(vii) the number of doses available in Canada.

Rather than implementing a broad vaccination program targeting farm workers and hunters, the CIQ recommends taking a shared decision-making approach by offering the Arepanrix™ H5N1 vaccine to:

(i) personnel working with the live virus (culture/isolate) and at influenza A(H5N1) vaccine production sites;

(ii) veterinarians, technicians, and staff who perform necropsies on potentially infected animals, and diagnostic laboratory personnel who come into contact with large numbers of potentially infected carcasses; and

(iii) workers who regularly participate in the management of cases on multiple farms, particularly through bird culling or building cleaning and disinfection; wildlife rehabilitation personnel; and workers who regularly come into close or prolonged contact with potentially infected animals or samples, according to the risk assessment carried out by the Direction générale de la protection de la santé publique of the MSSS.

These workers have a high probability of frequent and intense exposure to potentially infected wild or domestic birds.

Although Arepanrix™ H5N1 was tested with an interval of 21 days between the two doses, the CIQ recommends using a two-month interval, which would allow for a better immune response and a longer duration of protection (28). The minimum 21-day interval could be considered in the event of human-to-human transmission.

In the absence of data, the CIQ recommends that, insofar as possible, other vaccines not be administered at the same time as, or within six weeks before or after, the administration of a dose of Arepanrix™. This recommendation may be revised once additional data on co-administration become available. In this context, the first dose could be scheduled for the beginning of the summer season to ensure protection is in place for the fall migration.

The CIQ recommends this vaccination against A(H5N1) be evaluated, particularly with regard to:

1. the post-marketing **safety** of the vaccine, through **active surveillance** of the people who will be vaccinated, including during co-administration, if applicable. Ideally, this surveillance should be carried out in collaboration with the other Canadian provinces where the vaccine will be administered, to obtain a larger sample size;
2. the vaccine's **immunogenicity**: research is already planned as part of Professor Kanta Subbarao's work as a Canada Excellence Research Chair;
3. the **acceptability** of preventive measures, including vaccination, among the populations targeted in this guidance or who could potentially be targeted in the event of increased transmission of the virus;
4. **vaccination coverage**; and
5. the **logistical issues** associated with workplace vaccination of the target groups.

The CIQ will monitor developments in the epidemiology and research, and may amend its recommendations as knowledge evolves.

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APPENDIX 1 POPULATION ESTIMATES FOR DIFFERENT GROUPS OF WORKERS AT INCREASED RISK OF EXPOSURE TO THE AVIAN INFLUENZA A(H5N1) VIRUS

Table 4 People who handle the live avian influenza A(H5N1) virus in a laboratory setting

	Facilities	Number of workers
Laboratory workers who manipulate, handle, or culture the live avian influenza A(H5N1) virus	MAPAQ	• MAPAQ (Saint-Hyacinthe and Québec City) and necropsy suite at the Université de Montréal Faculty of Veterinary Medicine (FMV) 31 persons • FMV: CL2 zones – low risk; if biosafety breach has occurred: 35 persons • CL3 laboratory (Infectious Disease Research Centre, CHUL): 30 persons • CL3 laboratory (Quebec public health laboratory, LSPQ): 5 persons
	Université de Montréal	• Centre québécois sur la santé des animaux sauvages: 17 persons
	GSK, Sainte-Foy site	• 700

Table 5 Larger population groups exposed to birds or other animals, or to their environment, which could be a source of transmission to humans if the animals are infected

	Facilities	Number of workers
Poultry workers and residents of poultry farms	Chickens: 1,051 (50) Turkeys: 261 (50) Eggs: 1,171 (51) Farm birds: 76 (52) Poultry farming services: 19[a] Washing, disinfection, fumigation: 14[b]	3,269 (across 710 facilities)[a] 662[a] 54–89
Livestock workers and residents of livestock farms	Milk (quotas): 4,333 (53) Milk collectors/testers: N/A Inseminators: 200[b]	11,731[a] N/A N/A
Slaughter plant workers	N/A	N/A
Processing plant workers[c]	N/A	N/A
Individuals involved in poultry culling at farms with active avian influenza A(H5N1) outbreaks	Depopulation: 1[b] Bio-containment: 2 Composting: 2	11[a] 414 107
Wildlife protection officers	MELCCFP	330[d]
Wildlife rehabilitation staff, researchers, or people handling wild birds	Wildlife protection centres: 18 centres Researchers: 260 permits issued	180–360[e] 2,600[f]
Veterinarians and veterinary technicians	Veterinarians: MAPAQ cattle farms Avian practice Large animal practice Technicians: N/A	 14[b] 21 (54) 345 (54) N/A
Hunters and trappers	N/A	N/A
Indigenous hunters and their families (who participate in the plucking, butchering, etc. of birds) who make a living from hunting wild birds	N/A	N/A
People who process wild game or birds for food	N/A	N/A

Table 5 Larger population groups exposed to birds or other animals, or to their environment, which could be a source of transmission to humans if the animals are infected (continued)

	Facilities	Number of workers
Non-commercial farmers (for example, people who keep poultry in urban settings)	N/A	N/A

[a] SISAT: *Système d'information en santé au travail* [occupational health information system]

[b] MAPAQ: the Ministère de l'Agriculture, des Pêcheries et de l'Alimentation du Québec, from which some veterinarians and inspectors may be called upon to intervene on a cattle farm with a confirmed case

[c] Plant workers are only exposed if the animals have been missed by surveillance measures or if the plants are designated and equipped to receive milk from a positive farm. Ideally, only a few pre-identified plants will be designated to receive potentially contaminated milk from farms experiencing outbreaks. However, other plants could receive potentially contaminated milk from farms that have not yet been flagged as suspect or affected by an outbreak.

[d] MELCCFP: the Ministère de l'Environnement, de la Lutte aux changements climatiques, de la Faune et des Parcs, including ministry staff who handle wild birds

[e] Estimate based on 10 to 20 people per facility holding a native wildlife rehabilitation permit.

[f] Estimate based on 10 people per holder of a Canadian Wildlife Service migratory bird banding permit.

N/A: not available

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