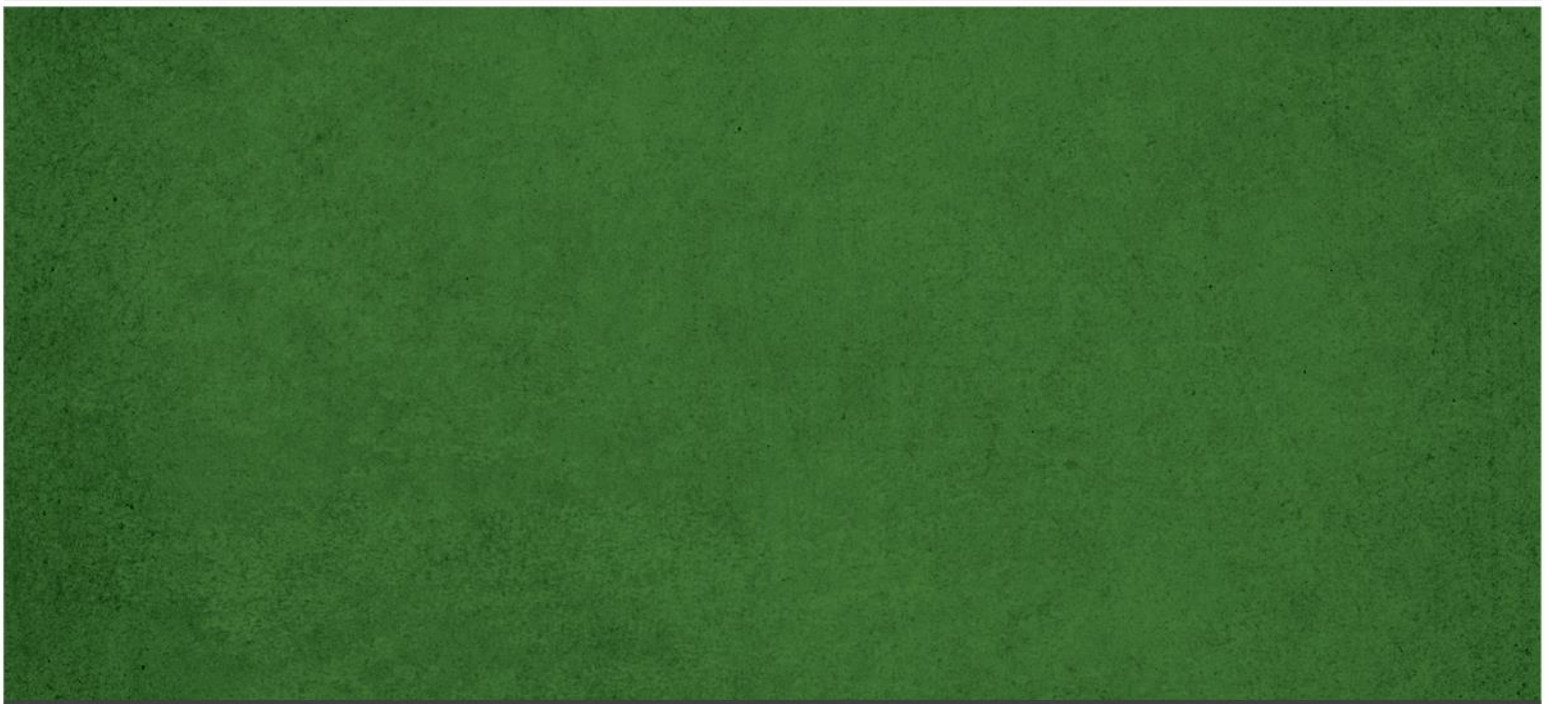
An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

NACI rapid response: Preliminary guidance on human vaccination against avian influenza in a non-pandemic context as of December 2024



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Preamble

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing, and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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Introduction

The current global outbreak of highly pathogenic avian influenza (HPAI) A(H5N1) is unprecedented, with widespread infections in wild birds, poultry, and numerous mammals across Canada, the United States (US), and other regions. Since March 2024, the US has reported ongoing transmission among dairy cattle. The risk of exposure and transmission to humans through contact with birds, other animals, or their environments has also increased. In the US, as of December 19, 2024, 61 human cases of avian influenza A(H5N1) have been confirmed in 2024, mainly among dairy and poultry workers, with 1 severe case [(1)]. In Canada, a single, severe human case has been reported in 2024 [(2)]. Two of the human cases in the US and the one in Canada have had unknown exposure sources.

Reports of transmission of avian influenza A(H5N1) viruses among birds and mammals have continued to increase globally. Considering the potential for animal-to-human (i.e., zoonotic) and human-to-human transmission, organizations across the Government of Canada, such as the Public Health Agency of Canada (PHAC), the Canadian Food Inspection Agency (CFIA), Environment and Climate Change Canada (ECCC), and Health Canada (HC), are working collaboratively to address avian influenza A(H5N1) through a One Health approach, which integrates human, animal, and environmental health perspectives. Strategies have included: surveillance of avian influenza A(H5N1) in wild birds and other wildlife, poultry, swine, cattle, and commercial milk samples; animal importation requirements; reinforcement of biosecurity measures (including the use of personal protective measures [PPE]) on farms); rapid response to managing poultry operations affected by outbreaks, including poultry culling and environmental disinfection; and monitoring and management of humans exposed on affected premises. For details on Canada's prevention, preparedness, and response initiatives, refer to Avian influenza A(H5N1): Canada's response. For details on initiatives in other countries, refer to: World Health Organization (WHO): Preparing for containment and mitigation of pandemic H5N1 influenza, Centers for Disease Control and Prevention (CDC): Bird flu outbreak response, and European Centre for Disease Prevention and Control (ECDC): Strategies and guidelines on avian influenza.

Considering the current epidemiological situation, several countries (including Canada, European Union (EU) countries, the United Kingdom (UK), and the US) are boosting surveillance activities, securing doses of human vaccines against avian influenza (HVAI), and preparing for the possible use of HVAI to prevent and respond to avian influenza A(H5N1) outbreaks. As of December 19, 2024, Finland is the only country to offer HVAI to populations at higher risk of exposure, as a response to outbreaks on fur farms [(3)]. HVAI can support a proactive public health response and strengthen Canada's preparedness by complementing other efforts to prevent or reduce the impact of avian influenza A(H5N1).

Objective

This rapid response was undertaken by NACI to provide expert advice and preliminary guidance for the potential use of HVAI in a non-pandemic context, as well as outline a framework for provincial and territorial health authority decision-making around HVAI use. The section entitled Specific guidance on the use of Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b) provides recommendations and guidance for possible use of this recently authorized HVAI by provincial and territorial public health authorities in foreseeable scenarios based on the evolving situation

in Canada and the US. A summary of the characteristics of Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b) can be found in Appendix A.

This statement provides guidance on the use of HVAI specific to a non-pandemic context and does not provide guidance for scenarios of human-to-human transmission or for a pandemic declared by the WHO (e.g., it does not provide guidance on the use of HVAI as an interim measure while awaiting the availability of a specific pandemic vaccine). Should these circumstances arise, NACI will provide further guidance. For additional information on outbreak management principles beyond immunization, as well as guidance on immunization during an influenza pandemic, refer to the Guidance on human health issues related to avian influenza in Canada and Canadian Pandemic Influenza Preparedness: Planning guidance for the health sector.

Methods

In brief, the broad stages in the preparation of this NACI statement were:

1. Analysis of the epidemiological situation in animals and humans globally, including in Canada and the US
2. Knowledge synthesis: retrieval and summary of individual studies, outbreak investigation reports, surveillance dashboards and websites, and grey literature
3. Synthesis of the body of evidence on benefits and harms, including identification of specific knowledge gaps and research priorities
4. Use of a published, peer-reviewed framework and evidence-informed tools to ensure that issues related to ethics, equity, feasibility, and acceptability (EEFA) are systematically assessed and integrated into the guidance [4]

For more information, please see NACI's evidence-based methods.

The following policy questions proposed to NACI are addressed in this statement:

- What are the objectives of human vaccination against avian influenza (HVAI) in a non-pandemic context?
- Which vaccination strategies, if any, should be employed in the current and potential future scenarios?
- If deployed, how should HVAI be used in the context of existing seasonal vaccine programs?

For this advisory committee statement, NACI reviewed the available evidence and key considerations as proposed by the NACI Influenza Working Group (IWG), including epidemiology and burden of disease, clinical evidence on HVAI (i.e., immunogenicity and safety), EEFA considerations according to the NACI peer-reviewed EEFA framework, and other aspects of the overall immunization strategy. A health economic analysis was not conducted as it was not deemed necessary for this preliminary guidance. Knowledge synthesis was performed by the NACI Secretariat and supervised by the IWG.

NACI consulted the Public Health Ethics Consultative Group (PHECG) about ethical considerations related to waiting for later use once certain triggers are met versus deploying a supply of HVAI in Canada once it is available. As well, the Canadian Immunization Committee

(CIC) was consulted for feedback from Canadian jurisdictions on the acceptability and feasibility of HVAI deployment.

Following a comprehensive review and discussions on September 18, 2024 and November 20, 2024, NACI approved this guidance. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text and are current as of December 19, 2024 when NACI finalized this document. NACI continues to monitor the evidence on the potential use of HVAI as well as the evolving epidemiological situation and will update its recommendations as needed.

Epidemiology

Background on avian influenza virology and the current A(H5N1) outbreak

Influenza A viruses are categorized by surface glycoproteins hemagglutinin (HA) and neuraminidase (NA), with 19 HA and 11 NA subtypes that can occur in numerous combinations (e.g., H1N1, H3N2, H5N1) [5]. The segmented genome of influenza A viruses enables reassortment (i.e., genetic shift), where viruses exchange genetic material to create novel strains. Additionally, as with other RNA viruses, viral RNA replication enzymes are highly error prone, resulting in high mutation rates (i.e., genetic drift). Currently in humans, seasonal influenza A viruses are A(H3N2) and A(H1N1) subtypes, while in birds many other subtypes can circulate. Wild aquatic birds are the primary reservoir for avian influenza and can carry the viruses without clinical signs of infection; however, the current outbreak of avian influenza A(H5N1) has caused higher mortality in some species [6]. Domestic poultry that acquire avian influenza are more likely to develop significant disease. Avian influenza viruses are classified as low pathogenic avian influenza (LPAI) if they cause no or only mild illness in chickens/poultry, or highly pathogenic avian influenza (HPAI) if they cause severe illness and high mortality in chickens/poultry [7]. Some LPAI strains can undergo adaptive mutations or reassortment events and evolve into HPAI. Infected birds spread the virus through feces, saliva, and nasal secretions. Geographic expansion is enabled through migration of wild birds. Avian influenza viruses have demonstrated the ability to infect mammals, including humans. For details, refer to Guidance on human health issues related to avian influenza in Canada (HHAI).

The origin of currently circulating avian influenza A(H5N1) viruses can be traced back to the A/Goose/Guangdong/1/1996 strain that was isolated from domestic waterfowl in Southern China in 1996. In 1997, an avian influenza A(H5N1) outbreak in poultry in China and Hong Kong resulted in 18 human cases with 6 deaths and the culling of 1.6 million birds. Avian influenza A(H5N1) virus re-emerged in 2003, causing widespread poultry outbreaks in Asia, with subsequent spread by wild birds to Africa, the Middle East, and Europe in 2005 [8]. Because of genetic diversity in the H5 gene, a clade nomenclature system was introduced to further classify the viruses into related groups based on this gene. In addition, sequencing of the viral genome resulted in the determination of genotypes that further define the relatedness of viruses to each other [8]. Avian influenza A(H5N1) clade 2.3.4.4 viruses emerged in China in 2008 and have been circulating widely since 2014 [9]. In the following years, the A(H5) clade 2.3.4.4 further diversified into clades 2.3.4.4a to 2.3.4.4h, including clade 2.3.4.4b [5, 8]. From 2014 to 2016, reassortment events between avian influenza A(H5N1) viruses and other avian influenza strains resulted in A(H5N6) and A(H5N8) strains that circulated in birds in several areas, including North America [10]. In 2020, clade 2.3.4.4b viruses acquired an N1 gene of avian origin through

reassortment, leading to the avian influenza A(H5N1) clade 2.3.4.4b strain that became dominant and circulated in wild birds in Asia, Africa, Europe and the Middle East [8]. This strain was first identified in North America in December 2021 in Newfoundland and Labrador and thereafter spread within North America, as well as to Central and South America [5, 6]. Avian influenza A(H5N1) clade 2.3.4.4b viruses have continued to circulate widely, resulting in an unprecedented epizootic outbreak in wild birds, poultry, and a variety of mammals in many parts of the world. They have also caused rare human infections in some areas, including Canada and the US. A few other clades of avian influenza A(H5N1) continue to circulate in limited geographic areas [8].

Disease overview

The HA surface glycoprotein of avian influenza viruses preferentially binds to cells with α2,3-linked sialic acid receptors, which are common in the respiratory and gastrointestinal tracts of wild birds and domestic poultry, but are also found in humans on the conjunctiva [11] as well as in the lower respiratory tract [12, 13], and in dairy cattle in the mammary tissue [14]. The receptors that predominate in human upper airways are α2,6- linked sialic acid receptors to which human influenza A virus subtypes (e.g., H1N1 and H3N2) bind [15]. There is currently no evidence that avian influenza A(H5N1) clade 2.3.4.4b viruses can be transmitted from human to human; to do so efficiently, they are generally thought to need to acquire the ability to bind to α2,6- linked sialic acid receptors [16, 17].

Humans can become infected with avian influenza through direct contact with infected animals, their secretions and excretions, or contaminated environments. Because avian influenza A(H5N1) has never circulated widely in humans, population-level immunity in humans is expected to be minimal. A serological study in the US showed that individuals, including those vaccinated against seasonal influenza, had low antibody levels against the avian influenza A(H5N1) clade 2.3.4.4b strain, suggesting little to no preexisting immunity to this virus [18].

The clinical presentation of avian influenza A(H5N1) in humans ranges from mild symptoms such as cough, conjunctivitis and fever, to severe respiratory or neurological complications or death. Asymptomatic cases may also be possible. Historically, the case fatality rate (CFR) of reported avian influenza A(H5N1) was approximately 50%. Among the cases occurring in 2024 in the US and Canada, most have been mild, causing mainly conjunctivitis and/or upper respiratory symptoms. The severity of the currently circulating avian influenza A(H5N1) clade 2.3.4.4b viruses is uncertain, given that there has been a relatively small number of human cases, mainly among farm workers, most of whom received prompt oseltamivir treatment [19]. The impacts of the particular genotypes and route of exposure (e.g., conjunctiva of the eye versus the respiratory tract) on disease severity are currently unknown. Additionally, the impact of traditional risk factors for influenza complications (e.g., younger and older age and the presence of underlying medical conditions) on disease severity caused by the currently circulating strain is unknown. Historically, influenza pandemics have had different mortality patterns by age group than seasonal influenza; for example, the 1918 Spanish influenza pandemic was characterized by elevated mortality risk in young adults [20].

Antiviral medications can be used to treat avian influenza A(H5N1). Treatment should be initiated as soon as possible, ideally within 48 hours of symptom onset, but should still be used after 48 hours if indicated. Antiviral medication may also be used for post-exposure prophylaxis

in some circumstances. For more information on symptoms and treatment, refer to the Antiviral recommendations section of the Guidance on human health issues related to avian influenza in Canada (HHAI).

Global human and animal epidemiology

The avian influenza A(H5N1) clade 2.3.4.4b strain that emerged in 2020 continues to evolve and spread among an unprecedented number of wild and domestic bird and mammalian species, with detection of the virus on every continent except Australia [21]. For global epidemiological updates, refer to the WHO's Global Influenza Programme: Avian influenza A(H5N1).

Between January 1, 2003, and November 1, 2024, 939 human cases of avian influenza A(H5N1) and 464 associated deaths have been reported globally, reflecting a CFR of approximately 50% [22]. However, this may be an overestimate given that mild infections can go undetected and thus unreported. Prior to 2024, most human cases have resulted from direct contact with infected birds or their environments. Rare instances of limited human-to-human transmission of avian influenza A(H5N1) have previously been reported because of prolonged exposure; however, there has been no evidence of human-to-human transmission noted since 2007 [23].

In the US, avian influenza A(H5N1) clade 2.3.4.4b viruses have affected over 130 million poultry and 10,000 wild birds since 2022 and were detected in dairy cattle for the first time in March 2024 [1]. In October 2024, a pig tested positive for avian influenza A(H5N1) clade 2.3.4.4b genotype D1.2 [24].

The dairy cattle outbreak, which has been attributed to a novel genotype, B3.13 [5] has resulted in widespread transmission in cattle and some poultry in the US, accounting for most cattle and poultry infections between March and November 2024 [25]. The B3.13 genotype has also caused infections in other animals such as cats, raccoons, opossums [5], and alpacas [26]. As of December 19, 2024, 866 dairy herds have been affected in 16 US states, with the largest number reported in California [27]. The widespread transmission among dairy cattle is a rare example of mammal-to-mammal transmission of avian influenza, likely attributed to high viral loads in the mammary glands of infected cows which enable transmission from milk and via the milking process [5]. Movement of dairy cattle, equipment, or vehicles between farms also likely facilitated spread of the virus across numerous farms and states [28].

Testing of milk can provide information on the burden of the avian influenza A(H5N1) clade 2.3.4.4.b outbreak affecting dairy cattle. Viral RNA has been detected in pasteurized milk in the US, with one study finding avian influenza A(H5N1) clade 2.3.4.4 viral RNA in 20% of 297 pasteurized dairy product samples collected over 5 days in April 2024, representing 132 processors from 38 states; however, due to the effectiveness of the pasteurization process, no infectious virus was detected in any sample [29].

While infection in dairy cattle can result in reduced or abnormal milk production, decreased appetite and other symptoms, most cattle survive their infection; however, longer term impacts are still being assessed. Unlike with poultry outbreaks where culling of the animals is conducted

to control the outbreak, in dairy cattle outbreaks, most animals are not euthanized. As such, infectious virus can persist on the farm as infections spread in the herd, presenting a continued risk for human exposure during that time. Furthermore, early evidence suggests that influenza A(H5N1) may remain stable at room and refrigerator temperatures on surfaces for several days and in bulk raw milk for several weeks [30].

Human infections in the US have been relatively rare and generally mild. As of December 19, 2024, of the 61 human cases, 37 cases were linked to exposure to infected cattle, 21 cases were linked to infected poultry farms and culling operations, 1 case was linked to infected birds in backyard flocks, and 2 cases had an unknown exposure source [1]. Under-reporting is also possible. Limited evidence suggests that there may be the possibility of asymptomatic infection in humans. In an American serological study of workers on dairy farms with infected cattle, influenza A(H5) antibodies were detected in 8 of 115 workers (7%), 4 of whom did not report symptoms; however, it is possible that delays in information collection may have resulted in challenges in recalling mild symptoms [31, 32].

While most human cases in the US as of December 19, 2024, have been due to genotype B3.13, genotype D1.1 has recently been identified in severe cases in Canada (refer to Human and animal epidemiology in Canada) and Louisiana, as well as mild cases in Washington State. Genotype D1.1 has been circulating among wild birds and poultry in Canada and recently in the US. Though the Canadian case's source of exposure was unknown, the case in Louisiana was reported to have exposure to sick and dead birds in backyard flocks [33].

For US epidemiological updates, refer to the CDC H5 bird flu: Current situation and USDA detections of highly pathogenic avian influenza.

Globally, the public health risk remains low for the general population, but higher for those with unprotected exposure to infected animals. For risk assessment details, refer to the Updated joint assessment of recent influenza A(H5N1) virus events in animals and people from the Food and Agriculture Organization of the United Nations, the WHO, and the World Organisation for Animal Health.

Human and animal epidemiology in Canada

Since December 2021, Canada has experienced numerous avian influenza A(H5N1) outbreaks, impacting over 14 million domestic birds [34] and 3,400 wild birds and mammals as of December 19, 2024 [35]. The virus has been detected in wild birds in all provinces and territories, and wild mammals in 10 provinces and 1 territory [35]. Additionally, domestic mammal detections (2 cats and 1 dog) have been reported in 2 provinces [36].

Most cases of avian influenza A(H5N1) in domestic birds have occurred in commercial poultry operations across all provinces except Prince Edward Island. British Columbia (BC) has reported the largest number of infected premises [37]. No human cases have been reported among workers at affected premises. As of December 19, 2024, Canada has not detected avian influenza A(H5N1) in dairy cattle or raw or pasteurized milk [38], nor has there been any reported detection of the B3.13 genotype in any wild or domestic animals. As part of enhanced surveillance protocols, lactating dairy cattle imported from the US must test negative for the virus [39].

As of December 19, 2024, there has been one human case of avian influenza A(H5N1) acquired in Canada. In November 2024, a teenager in BC was hospitalized with acute respiratory distress syndrome and found to be infected with avian influenza A(H5N1) clade 2.3.4.4b. The source of exposure was unknown, as all tests of human and animal contacts and environmental samples were negative for influenza A(H5) [40]. Genetic sequencing identified the virus as genotype D1.1, a strain circulating in local poultry and wild birds in BC [2, 41]. Notably, sequencing of the virus found mutations that have been associated with mammalian adaptation and enhanced replication [17, 42, 43]. For Canadian epidemiological updates, refer to: Avian influenza (bird flu), Human Emerging Respiratory Pathogens Bulletin, Pandemic risk scenario analysis for influenza A(H5N1), Protocol for enhanced human surveillance of avian influenza A(H5N1) on farms in Canada, and PHAC's update on avian influenza and risk to Canadians.

Vaccines

Prior to 2025, Health Canada (HC) authorized two HVAI (both against A(H5N1)) for individuals 6 months of age and older based on immunogenicity studies assessed against standardized criteria for influenza vaccines. Both products are adjuvanted and administered as 2 doses given at least 21 days apart.

- Arepanrix™ H5N1 (A/Indonesia clade 2.1.3.2) is an AS03-adjuvanted inactivated HVAI manufactured by GSK. This vaccine was initially authorized for use in Canada in 2013 as a pandemic vaccine, based on immunogenicity and safety data from 6 randomized trials and 3 supportive studies [44].
- Foclivia® H5N1 (A/Vietnam clade 1) is an MF59-adjuvanted inactivated HVAI manufactured by Seqirus. This vaccine was authorized for use in Canada in 2021 as a pandemic vaccine, based on immunogenicity and safety data from 4 randomized-controlled trials (RCTs) and 6 supportive trials [45].

Although these vaccines have not been used in Canada, having authorized products accelerates subsequent regulatory processes if a strain change is required in the event of a pandemic.

Like WHO-led monitoring for seasonal influenza viruses, the WHO also monitors avian influenza strains. Based on ongoing surveillance and assessment processes, the WHO recommends candidate vaccine viruses (CVVs) for avian influenza strains that manufacturers can use to produce HVAI. Several CVVs for influenza A(H5) viruses have been recommended, some against earlier A(H5) clades and some against clade 2.3.4.4b in combination with either A(N1) or A(N8) [46]. Countries may choose to authorize one or more of these HVAI and procure them for potential use in a targeted vaccination program. The WHO-recommended CVVs that are more closely related to the avian influenza A(H5N1) clade 2.3.4.4b strains currently circulating in birds and mammals in North America include the A/Astrakhan/3212/2020 (H5N8)-like strain (CBER-RG8A) (subsequently referred to as H5N8 A/Astrakhan) and the A/American wigeon/South Carolina/22-000345-001/2021 (H5N1)-like strain (subsequently referred to as H5N1 A/American wigeon) [47]. Manufacturers are in various stages of vaccine development using these CVVs, which are anticipated to improve the immune response against the avian influenza A(H5N1) clade 2.3.4.4b strain currently circulating in animals in North America compared to CVVs against earlier clades.

Based on a WHO report from September 2024, genetic characterization of avian influenza A(H5N1) clade 2.3.4.4b viruses from human cases in the US have shown that they are genetically similar to the H5N1 A/American wigeon strain (for which there is a CVV), with between 2 and 6 amino acid substitutions. Antigenic testing showed that the human avian influenza A(H5N1) viruses reacted well to anti-sera produced in ferrets against the H5N1 A/American wigeon and H5N8 A/Astrakhan CVVs [48].

As part of pandemic preparedness efforts, the Government of Canada has procured a limited supply of at least 500,000 doses of Arepanrix™ H5N1 (A/American wigeon), expected to be allocated to provinces and territories in early 2025 to consider for potential use. A summary of the characteristics of this vaccine can be found in Appendix A. There were no clinical trial data specific for this CVV strain that were reviewed as part of the regulatory process. This vaccine was authorized as a strain change to Arepanrix™ H5N1 (A/Indonesia), and authorization was based on safety and immunogenicity studies conducted for Arepanrix™ H5N1 (A/Indonesia). This follows the standard practice for strain changes to seasonal influenza vaccines, as clinical trials are not required to support authorization of the annual strain change [49].

Subsequent sections of the statement contain information about the following vaccine products that provide indirect evidence relevant to Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b):

- Arepanrix™ H5N1 (A/Indonesia clade 2.1.3.2) (GSK)
- Foclivia® H5N1 (A/Vietnam clade 1) (Seqirus), and
- Two monovalent GSK-produced AS03-adjuvanted vaccines licensed for use during the 2009-2010 influenza A(H1N1) pandemic:
    - Arepanrix™ H1N1 pdm09, and
    - Pandemrix™ H1N1 pdm09.

When interpreting the indirect evidence, please note the following:

- Although immunogenicity criteria used to assess seasonal and pandemic influenza vaccines have been used for HVAI, the correlation of these criteria to efficacy/effectiveness of HVAI is unknown.
- Effectiveness data are only available for Arepanrix™ H1N1 and Pandemrix™ H1N1, as these were the only vaccines used outside of clinical trials and with sufficient circulating virus in the population to generate vaccine effectiveness estimates.

Immunogenicity of Arepanrix™ H5N1 (A/Indonesia clade 2.1.3.2)

The immunogenicity of Arepanrix™ H5N1 (A/Indonesia) was assessed in 6 randomized trials and 3 supportive studies, in which individuals were administered 2 doses of the vaccine intramuscularly 21 days apart (except in one study where different schedules were assessed). Humoral immune responses were measured with hemagglutination inhibition (HI) and virus neutralization assays [44].

Immunogenicity against the homologous strain (immune responses against the vaccine strain) using the HI assay

- In adults 18 years and older who received 2 doses (0.5 mL each) of vaccine, seroprotection rates (defined as the proportion of subjects with a HI titre ≥ 1:40) against the homologous

strain ranged from 76.8 to 91.0% 21 days after the second dose, and remained between 62.2 to 63.5% 6 months after the start of the series [44].

- In children 6 months to <18 years of age who received 2 doses (0.25 mL each) of vaccine, seroprotection rates ranged between 99 to 100% 21 days after the second dose and remained between 72.4 to 95.2% 6 months after the start of the series [50].
- Three studies (2 in adults and 1 in children) assessed the immune response against the homologous strain after 1 dose (on day 21). Most estimates following 1 dose did not meet the immunogenicity criteria used for authorization [51-53].

Immunogenicity against heterologous strains (immune responses against non-vaccine strains) using the HI assay

- The cross-reactivity of the immune response against heterologous avian influenza A(H5N1) strains (i.e. A/Vietnam/1194/2004, A/turkey/Turkey/1/2005, and A/Anhui/01/2005) was also evaluated. Two doses of Arepanrix™ H5N1 (A/Indonesia) appeared to induce some cross-reactive response to these heterologous strains, but HI responses were much lower against heterologous compared to homologous strains, particularly with respect to geometric mean titres (GMTs). Additionally, the immune responses appeared stronger against heterologous strains in the same clade as the vaccine strain than against those in different clades [44].
- Two studies in adults found that 1 dose of Arepanrix™ H5N1 (A/Indonesia) did not meet pre-defined immunogenicity criteria against heterologous strains when measured on day 21 [51, 52].

Overall, 2 doses of Arepanrix™ H5N1 (A/Indonesia) were highly immunogenic against the homologous strain, with some cross-reactive responses to heterologous strains. A recent American study found cross-neutralizing antibodies against a clade 2.3.4.4b strain in adults vaccinated with either 2 doses of Arepanrix™ H5N1 (A/Indonesia) or 3 doses of Foclivia® H5N1 (A/Vietnam), but it is unclear whether this cross-reactive response translates to clinical protection [54].

Efficacy/effectiveness of Arepanrix™ H1N1 pdm09

The AS03-adjuvanted monovalent Arepanrix™ H1N1 vaccine was widely used in Canada during the 2009 H1N1 pandemic. Three Canadian studies reported high effectiveness following vaccination with 1 dose (or 2 doses for some children) of this vaccine, ranging from 85% to 100%, against symptomatic laboratory-confirmed influenza or hospitalization [55-57]. The applicability of this finding to Arepanrix™ H5N1 (A/American wigeon) is uncertain. Although the adjuvant and concentration of antigen are the same between the H1N1 and H5N1 (A/American wigeon) products, extrapolation from one vaccine to the other may be limited due to the difference in subtypes (A(H1N1) subtypes have previously circulated in the human population, unlike A(H5N1)) and differences in the number of doses required to meet immunogenicity criteria (1 dose for the A(H1N1) product and 2 doses for the A(H5N1) product) between the vaccines.

Safety of Arepanrix™ H5N1 (A/Indonesia clade 2.1.3.2), Arepanrix™ H1N1 pdm09, and Pandemrix™ H1N1 pdm09

Arepanrix™ H5N1 (A/Indonesia clade 2.1.3.2)

Safety data from previous clinical trials conducted by the manufacturer showed that Arepanrix™ H5N1 (A/Indonesia) was generally well-tolerated. Adverse events reported following

immunization (AEFIs) were predominantly mild to moderate injection site reactions that resolved within a few days without sequelae, as well as muscle aches, headache, fatigue, and joint pain [44]. As the use of Arepanrix™ H5N1 (A/Indonesia) was limited to clinical trials, post-marketing safety data are unavailable.

Arepanrix™ H1N1 pdm09 and Pandemrix™ H1N1 pdm09

A GSK-supported safety review of Arepanrix™ H1N1 and Pandemrix™ H1N1 vaccines based on non-clinical, clinical, and post-licensure data noted that they were generally well tolerated with an acceptable safety profile, including in special populations (e.g., pregnant women, immunocompromised individuals) [58]. In Quebec, AEFI surveillance showed an increase in the rate of anaphylaxis following Arepanrix™ H1N1 vaccination compared to seasonal influenza vaccination [59]. Additionally, one study in Quebec and one study in Germany found a small increased risk of Guillain-Barré syndrome (GBS) following Arepanrix™ H1N1 and Pandemrix™ H1N1 [60, 61], but several other studies did not show an association with AS03-adjuvanted H1N1 vaccines and GBS. A notable safety signal (i.e., narcolepsy) was identified with Pandemrix™ H1N1, as described below.

Narcolepsy following Pandemrix™ H1N1 pdm09

Narcolepsy is a neurological disorder that affects sleep-wake cycles and causes excessive daytime sleepiness. Following the 2009-2010 influenza A(H1N1) pandemic immunization campaigns, Pandemrix™ H1N1 was found to be associated with an increase in the incidence of narcolepsy cases among children and adolescents in Sweden and Finland (with relative risk in those 5 to 19 years of age of 7.5 (95% confidence interval [CI]: 5.2 to 10.7) and 6.4 (95% CI: 4.2 to 9.7) respectively, compared to pre-pandemic rates) [62], as well as in several other European countries [63]. In Canada, a Quebec-based study showed a possible but inconclusive link between Arepanrix™ H1N1 and narcolepsy [64], while other Canadian studies found no association [65, 66]. Overall, evidence suggested a strong link between Pandemrix™ H1N1 and narcolepsy in younger populations in some countries, whereas Arepanrix™ H1N1 showed minimal to no such association.

Mechanisms to explain the connection between Pandemrix™ H1N1 and narcolepsy are unclear, but hypotheses have suggested the role of "molecular mimicry," where a vaccine antigen triggers a CD4 T-cell mediated immune response that impacts the narcolepsy-related protein hypocretin [58, 67-69]. Some studies have assessed differences in the manufacturing process and proteins contained in the influenza A(H1N1) pdm09 vaccines to attempt to explain why narcolepsy appeared to be related to Pandemrix™ H1N1 and not Arepanrix™ H1N1 [67, 70].

No link between AS03 and narcolepsy has been found with any other AS03-adjuvanted vaccines. This includes an AS03-adjuvanted COVID-19 vaccine, Vidprevtyn Beta, given to over 2 million adults in Europe (mainly in England) [71], as well as several other AS03-adjuvanted vaccines evaluated in early to late phase clinical trials [50, 72-74].

Concurrent administration with other vaccines

There are no data on concurrent administration of Arepanrix™ H5N1 (A/American wigeon). As per the product monograph, Fodivia® H5N1 (A/Vietnam) can be concurrently administered with non-adjuvanted seasonal vaccines if given in separate limbs [45]. Additionally, existing studies suggest that Arepanrix™ H1N1 is generally safe when concurrently administered with seasonal

influenza vaccines, though some evidence indicates a reduced immune response to the A(H1N1) strain in certain scenarios, with unclear clinical significance [75, 76].

Seasonal influenza vaccination

NACI reiterates its recommendation that all individuals 6 months of age and older should receive an authorized, age-appropriate seasonal influenza vaccine. This includes people whose occupational or recreational activities increase their risk of exposure to avian influenza A(H5N1) viruses.

Seasonal influenza vaccines target influenza A subtypes H3N2 and H1N1 and one or two lineages of influenza B. Although seasonal influenza vaccines do not protect against avian influenza A(H5N1) viruses, they may mitigate the severity of seasonal influenza and reduce the risk of co-infection with seasonal and avian influenza strains. Refer to the NACI statements on seasonal influenza vaccines for details.

Ethics, equity, feasibility, and acceptability

Ethical considerations

NACI considered various public health ethical principles and consulted with the Public Health Ethics Consultative Group (PHECG) when formulating recommendations for the possible use of HVAI in a non-pandemic context. For details on PHECG processes, refer to the Framework for ethical deliberation and decision-making in public health (PDF). A clear public health objective is crucial to guide decision-making on the use of HVAI use (refer to the Objective of using HVAI in a non-pandemic context). The decision regarding whether to use HVAI weighs known data about the virus and the ability of HVAI to meet public health objectives, alongside assessments of scientific, social, and economic risks of avian influenza A(H5N1) infection. NACI acknowledges the importance of transparency regarding known and unknown factors, as well as transparency behind decisions to use or not use HVAI, to maintain public trust.

Equity considerations

If a HVAI program is implemented, provinces and territories should consider and address potential communication and vaccination accessibility challenges for individuals at increased risk of exposure to avian influenza A(H5N1). For example, the poultry and cattle farm workforce, which includes seasonal migrant workers, may experience barriers to accessing vaccines and health services due to factors such as rural residence, language barriers, lack of information, and/or misinformation. Enhancing understanding of barriers to access and incorporating key populations' perspectives into decision-making can help identify and address health equity gaps.

Feasibility considerations

NACI consulted with the Canadian Immunization Committee (CIC) regarding the feasibility of a potential HVAI program in a non-pandemic context. Overall, no significant issues were identified for feasibility implications that could impact decision making for this guidance. Potential considerations that were noted related to overall program costs; vaccine availability, storage, and handling; and immunizer training and availability. Addressing feasibility factors, including how to manage a potential HVAI vaccine program alongside other public health priorities and

longstanding vaccination programs, will remain important as future evidence emerges on this topic.

Acceptability considerations

There is currently no evidence available about the acceptability of HVAI in a non-pandemic context in Canada. Furthermore, national seasonal influenza vaccine coverage rates stratified by occupational groups are unavailable. However, some indirect evidence exists. Previous studies have reported lower seasonal influenza vaccine uptake among children and adults in rural areas of Canada [77, 78], where there may be increased risk of avian influenza A(H5N1) exposure due to agricultural activities. Engagement with individuals at higher exposure risk of avian influenza A(H5N1), such as agricultural sector workers and representatives, will be important in ensuring the effective delivery of a HVAI program. Moreover, vaccine acceptability may be supported by providing clear communication about the purpose and potential benefits and risks of vaccination, as well as easy access to vaccination opportunities. Because vaccine allocation is not NACI's responsibility, EEFA considerations around allocation were not addressed. Allocation of HVAI to provinces and territories is discussed in the Additional information on allocation considerations section. Although the use of HVAI doses allocated to a province or territory is that jurisdiction's responsibility, collaboration, communication, and transparency in decision making across Canadian jurisdictions are important to support acceptability.

In June 2024, Finland was the first (and as of December 19, 2024, the only) country to launch an immunization program with HVAI. Their program targets individuals at increased risk of contracting avian influenza, such as workers on fur and poultry farms, veterinarians and laboratory workers, bird-ringers, and close contacts of suspected or confirmed human cases. As of December 7, 2024, 5% of the eligible population had received the 2-dose vaccine series [(79)]. The generalizability of Finland's vaccination campaign to a HVAI program in Canada is unclear. Behavioural science studies are ongoing in Finland to determine what can be learned from their experience.

Objective of using HVAI in a non-pandemic context

As requested by PHAC, NACI discussed the objective for the use of HVAI in a non-pandemic context to guide the development of a framework for potential use of HVAI to aid in provincial and territorial health authority decision-making. NACI proposes that the objective for the potential use of currently authorized HVAI is to prevent human infection with avian influenza A(H5N1) viruses. Preventing transmission from animals to humans could help prevent severe disease in humans and limit opportunities for viral adaptations that could facilitate human-to-human transmission.

NACI's considerations in arriving at this objective are summarized in Appendix B.

Recommendations

Consistent with the above objective for using HVAI in a non-pandemic context and following a review of available evidence and EEFA considerations summarized above, NACI makes the following recommendations for public health level decision-making as of December 2024. These recommendations provide a general framework for provincial and territorial health authorities to aid in decision-making about whether, when, and for whom HVAI may be used in a non-pandemic context, to support the objective of preventing human infection with avian influenza A(H5N1) viruses. Specific recommendations, guidance, considerations, and supporting information on the use of Arepanrix™ H5N1 (A/American wigeon), which could potentially be used in Canada in foreseeable epidemiologic contexts, is provided in the section entitled Specific guidance on the use of Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b).

NACI will continue to carefully monitor the epidemiology of avian influenza in animals and humans, scientific developments, and evidence related to HVAI (including emerging vaccine immunogenicity and safety data), and will update its recommendations as needed.

Recommendation 1. NACI identifies the following factors for federal, provincial, and territorial authorities to consider when deciding whether and when to use human vaccines against avian influenza (HVAI) in a non-pandemic context:

Table 1. Factors to consider in deciding whether and when to use HVAI

Factors	Considerations regarding whether and when to use HVAI
Human	• Increasing numbers of human cases and the rate of increase of cases • Source of human cases (e.g., zoonotic, unknown, or possible human-to-human transmission) • Severity of human cases (including clinical manifestations and frequency of severe outcomes)
Animal	• Involvement of poultry, dairy cattle, swine, or other similar zoonotic risk that may increase risk of exposure at the animal/human interface and the extent of detection in these animals • Detection (and the extent of detection) of viral RNA in the milk supply in Canada
Virologic factors and animal studies	• Detection of mutations/virologic properties that could increase the risk of human infection, transmission, and/or severe disease • Animal studies that suggest increased transmissibility or disease severity • Emergence of antiviral resistance

In assessing the factors in Table 1, consideration should be given to the following:

- Human, animal and virological factors, as well as emerging findings from animal studies will occur in various combinations; judgement will be required in the context of evolving scenarios based on the combinations of these factors.
- Human factors are most likely to influence decisions due to the limited understanding of the implications of animal factors, virologic factors, and animal studies.

- The location/jurisdiction of human and animal cases (e.g., whether they occur within or outside of Canada; if not within Canada, the likelihood that they will also occur in Canada; if within Canada, the affected location(s)/jurisdiction(s) within the country, including in bordering jurisdictions).
- The magnitude and trends in the frequency of the factors (e.g., how many cases or detections over what time frame and in what geographic area; the frequency of severe outcomes; the extent of different modes of spread).

Recommendation 2. NACI identifies the following key populations to prioritize for possible use of HVAI, depending on the evolving avian influenza A(H5N1) situation in a non-pandemic context:

Table 2. Key populations to prioritize for possible use of HVAI

Key populations[a]		Examples
1	People who handle live avian influenza A(H5N1) virus in laboratory settings	Laboratory workers who manipulate, handle, or culture live avian influenza A(H5N1) virus such as in research, industrial, or clinical reference laboratory settings
2	People with ongoing contact with known infected birds or other known infected animals or their environments	Those involved in poultry and other bird culling; workers or residents on poultry, dairy, and other farms/premises with active avian influenza A(H5N1) outbreaks; wildlife officers, researchers, and rehabilitators, and veterinarians or veterinary technicians who are exposed to dead or sick birds or mammals with avian influenza A(H5N1)
3	Individuals who work or live on farms with geographic or other connection to farms experiencing outbreaks (such that these connections result in potential exposure risks)	Workers or residents on farms in a community or region of an affected farm; workers within a primary control zone around an affected farm[b]; workers who have epidemiological links to affected farms including shared suppliers or equipment, or via transportation vehicles or movement of cattle to other farms, or exposure to raw milk
4	Larger population groups with exposure to birds or other animals or their environments which, if these animals were infected, have the potential to be a source for transmission to humans	Poultry and livestock workers and residents on these farms; slaughterhouse and processing plant workers; workers who transport livestock; wildlife officers, wildlife researchers, and wildlife rehabilitators; veterinarians and veterinary technicians; hunters and trappers; people who process wild game or birds for food; non-commercial farm operators or hobbyists (e.g., people with backyard flocks, exhibition farms)

[a] Key populations are listed in descending order of risk of exposure to A(H5N1) based on current epidemiology. These populations have been identified based on their known or potential risk of exposure to known sources of avian influenza A(H5N1) (i.e., sources where a risk of transmission to humans has been identified), and not according to increased risk of influenza-related complications in the individual (e.g., not due to age or underlying medical conditions).

[b] To prevent the spread of avian influenza, the CFIA establishes primary control zones within approximately a 10 km radius of a premises where avian influenza infection has been detected.

Summary of evidence, rationale, and additional considerations:

- Laboratory workers who handle live avian influenza viruses potentially have increased risk of prolonged exposure to high concentrations of the virus. HVAI could provide another protective measure in addition to laboratory safety protocols.
- The majority of cases of avian influenza A(H5N1) clade 2.3.4.4b in North America in 2024 have occurred among people exposed to infected poultry or cattle or their environments. HVAI could provide another protective measure in addition to PPE and other biosecurity measures.
- The use of HVAI in close contacts or secondary contacts (i.e., contacts of close contacts) of human cases of avian influenza A(H5N1) was considered to likely be an impractical approach due to the short time period after exposure to the primary case for secondary cases of influenza to become ill and infectious to others (based mainly on experience with seasonal influenza). NACI will continue to monitor emerging evidence about the incubation period of avian influenza A(H5N1) in humans and update recommendations if indicated.
- This guidance does not address the use of HVAI in broader populations nor its potential use as an interim measure during a pandemic if a specific pandemic vaccine is unavailable. Should evidence of human-to-human transmission arise, NACI will issue updated guidance.

Recommendation 3. NACI recommends that it is preferable to have an interval of at least 6 weeks separating HVAI and any other vaccine, unless HVAI or another vaccine is needed urgently. This recommendation is precautionary to prevent erroneous attribution of an adverse event following immunization (AEFI) to one particular vaccine or the other.

Summary of evidence, rationale, and additional considerations:

- In general, as per the Timing of vaccine administration chapter in the Canadian Immunization Guide (CIG), concurrent administration of inactivated vaccines with other inactivated or live vaccines is supported; however, given the limited evidence currently available, this suggested waiting period between vaccines is precautionary to facilitate the investigation of any adverse events that may arise.
- There were no safety signals from studies on concurrent administration of Foclivia® H5N1 (A/Vietnam) or Arepanrix™ H1N1 with unadjuvanted seasonal influenza vaccines.
- The 6-week interval between vaccines should not delay a HVAI vaccine that is needed urgently. As well, this interval may be challenging for some individuals who may require timely protection against several diseases, such as during respiratory virus season or for post-exposure prophylaxis for non-influenza diseases. Concurrent administration or a shortened interval between HVAI and other vaccines may be warranted in some individual circumstances at the clinical discretion of the prescribing healthcare provider.

Specific guidance on the use of Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b)

The following recommendation for the potential use of Arepanrix™ H5N1 (A/American wigeon) supplements NACI's overarching guidance outlined above on the use of HVAI for public health level decision-making. This section includes a decision-aid matrix with sample scenarios based on foreseeable scenarios, considering the evolving epidemiology in Canada and the US. Key information regarding Arepanrix™ H5N1 (A/American wigeon) can be found in Appendix A.

NACI notes that decisions regarding the use of HVAI are context-specific and require consideration of the extent and geographic distribution of animal and human cases, as well as risk-benefit analyses for the individual, including access to and effectiveness of antiviral treatment, and other local programmatic and operational factors (e.g., current immunization programs, resources and outbreak control measures).

Additional information on the strength of NACI recommendations is available in Table 4.

Recommendation 4. NACI recommends that Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b) may be offered as a 2-dose series to individuals 6 months of age and older in specific circumstances. [Discretionary NACI recommendation]

To support provinces and territories in deciding whether and when to use this product, NACI has provided factors to consider in Table 1 and key populations to prioritize for possible HVAI use in Table 2, as well as guidance in a decision-aid for 3 foreseeable sample jurisdiction-specific scenarios (Table 3):

Table 3. Decision-aid matrix for human vaccines against avian influenza (HVAI) use in 3 foreseeable sample scenarios in key populations

Sample jurisdiction-specific scenarios[a]	People who handle live avian influenza A(H5N1) virus in laboratory settings	People with ongoing contact with known infected birds or other known infected animals or their environments	Individuals who work or live on farms with geographic or other connection to farms experiencing outbreaks (such that these connections result in potential exposure risks)	Larger population groups with exposure to birds or other animals or their environments which, if these animals were infected, have the potential to be a source for transmission to humans
Scenario 1: **a)** No or very infrequent human cases; and **b)** poultry outbreaks; and **c)** no dairy cattle involvement	Consider use	Consider use	Not recommended	Not recommended
Scenario 2: **a)** No or very infrequent human cases; and **b)** poultry outbreaks; and **c)** dairy cattle involvement	Consider use	Consider use	Consider use	Consider use in some circumstances[b]
Scenario 3: **a)** Increasing number of human cases (greater than Scenario 2); all/almost all are zoonotic; all/almost all are mild; and **b)** poultry outbreaks and/or dairy cattle involvement	Consider use	Consider use / Use in some circumstances[c]	Consider use / Use in some circumstances[c]	Consider use / Use in some circumstances[c]

[a] When assessing scenarios, jurisdictions may consider the situation in bordering jurisdictions as well.

[b] Depending on the extent and geographic distribution of dairy farms with outbreaks, broader vaccination of dairy farm workers and those who live on farms can be considered (i.e., vaccination of some dairy farm workers and those who live on farms with no connections to specific outbreaks).

[c] Depending on the extent of human cases and their geographic distribution, there may be some groups for whom vaccine is warranted. For example, if multiple human cases arise from dairy cattle exposures in a particular region, that jurisdiction could offer vaccine to individuals working on, living on or associated with farms experiencing outbreaks and could consider broadening the eligibility to offer vaccine to other dairy farmers and those who live on dairy farms (beyond those connected to infected dairy farms). These decisions are context-specific and require judgement based on the particular scenario.

Summary of evidence, rationale, and additional considerations:

- Based on available indirect evidence, Arepanrix™ H5N1 (A/American wigeon) is expected to be immunogenic against avian influenza A(H5N1) clade 2.3.4.4b viruses. Clinical trials of similar A(H5N1) products have shown no safety signals, recognizing that sample sizes in clinical trials are relatively small. NACI will continue to monitor emerging evidence and update guidance on HVAI as warranted.
- As noted above, NACI recommends that, in a non-pandemic context, the objective of using HVAI is to prevent human infections with avian influenza A(H5N1) viruses. Preventing transmission from animals to humans could help prevent severe disease in humans and limit opportunities for viral adaptations that could facilitate human-to-human transmission.
- Key populations have been identified due to their known or potential risk of exposure to known sources of avian influenza A(H5N1) (i.e., sources where a risk of transmission to humans has been identified).
- Scenario 2 includes dairy cattle involvement in Canada which could result in widespread outbreaks in cattle with spread to other animals, as has been the case in the US. Dairy cattle involvement may represent increased risk for human exposure because, unlike poultry outbreaks, dairy cattle on premises with an avian influenza A(H5N1) outbreak are not systematically culled. People who have contacts with infected dairy cattle or their environments may experience prolonged exposure to avian influenza A(H5N1) via direct contact or through contaminated milk or surfaces, resulting in increased risk of human infection.
- HVAI could provide another protective measure in addition to biosecurity measures on farms and PPE and other laboratory protocols in laboratory settings.
- This guidance does not address the use of HVAI in broader populations nor its potential use as an interim measure during a pandemic if a specific pandemic vaccine is unavailable. Should evidence of human-to-human transmission arise, NACI will issue updated guidance.

Table 4. Strength of NACI recommendations

Strength of NACI recommendation (based on factors not isolated to strength of evidence, e.g., public health need)	Strong	Discretionary
Wording	"Should/should not be offered"	"May/may not be offered"
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages ("should"); OR known/anticipated disadvantages outweigh known/anticipated advantages ("should not")	Known/anticipated advantages closely balanced with known/anticipated disadvantages; OR uncertainty in the evidence of advantages and disadvantages exists
Implication	A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present	A discretionary recommendation may be considered for some populations/individuals in some circumstances; Alternative approaches may be reasonable

Additional information on allocation considerations

PHAC is developing a flexible allocation framework to support equitable distribution among jurisdictions, which includes current and historical epidemiological trends of avian influenza A(H5N1) on farms provided via the CFIA, labour statistics for employment-related risk groups, and census division demographic data to determine wider population risk associated with proximity to livestock production. This allocation approach would differ from a per capita approach, such as the one implemented for the COVID-19 vaccine distribution, as the distribution of at-risk populations listed in this document may represent varying proportions of the population across jurisdictions.

Knowledge gaps and research priorities

After review of the existing evidence, NACI has identified the need for further research to address current knowledge gaps where data are absent or limited. NACI recognizes that there are studies already in progress that may address some of these gaps, but the findings of these studies were not available at the time of review. Knowledge gaps and priority areas for research are listed below.

Vaccine efficacy/effectiveness, immunogenicity, and safety

- Pre-authorization immunogenicity and safety data for strain-updated HVAI
- Post-authorization effectiveness, safety, and immunogenicity data on any HVAI that are used beyond the clinical trials, including the duration of protection and/or the duration of the immune response
- Efficacy/effectiveness and immunogenicity after 1 dose of HVAI
- Need for and optimal timing of second dose

- Breadth of the immune response conferred by the vaccine, including understanding of the degree of cross-reactive immune response against heterologous avian influenza A(H5N1) strains
- Safety and immunogenicity of concurrent administration
- Safety profile in large populations and subgroups not included in clinical trials
- Determining correlates of protection for avian influenza A(H5N1)
- Understanding the role of pre-existing immunity in protection
- Understanding the role of cross-protection from seasonal influenza vaccine
- Understanding the role of the neuraminidase glycoprotein in providing protection across all circulating neuraminidase subtypes and genotypes
- Characterization of viral evolution following the implementation of vaccination (e.g., vaccine escape)
- Research into influenza vaccines that offer broader strain protection and/or longer duration of protection, including using novel vaccine platforms

Epidemiology

- Infectious dose and types of exposure necessary (intensity, duration) to induce human infection following contact with infected livestock, birds, and contaminated products or environments
- Determination of key parameters in the event of human-to-human transmission
- Effectiveness of biosecurity measures to prevent transmission among animals and from animals to humans in the dairy/cattle and poultry industries and challenges in their consistent implementation
- Pathogenicity of the circulating virus in humans, including identification of risk factors for severe outcomes (e.g., age, medical conditions)
- Potential uses of wastewater surveillance to inform decision-making
- Monitoring virological features/changes that increase transmissibility to or between humans, affect severity, or confer resistance to antiviral medication
- Monitoring studies in animal models that may have implications for understanding disease severity in humans
- Understanding the frequency of asymptomatic infections

Ethics, equity, feasibility, and acceptability

- Acceptability of HVAI if offered to key populations
- Feasibility of targeting HVAI programs for key populations, including costs and opportunity costs of implementing potential HVAI programs

For further information on priority knowledge gaps and research needs recognized by PHAC, refer to Avian influenza A(H5Nx): Public health knowledge gaps and research needs.

List of abbreviations

AEFI	Adverse event following immunization
BC	British Columbia
CFIA	Canadian Food Inspection Agency
CFR	Case fatality rate
CI	Confidence interval
CIC	Canadian Immunization Committee
CVV	Candidate vaccine virus
ECCC	Environment and Climate Change Canada
EEFA	Ethics, equity, feasibility, acceptability
EU	European Union
GBS	Guillain-Barré syndrome
GMT	Geometric mean titre
HA	Hemagglutinin
HC	Health Canada
HI	Hemagglutination inhibition
HPAI	Highly pathogenic avian influenza
HVAI	Human vaccines against avian influenza
IWG	Influenza Working Group
LPAI	Low pathogenic avian influenza
NA	Neuraminidase
NACI	National Advisory Committee on Immunization
pdm09	Pandemic 2009 H1N1 influenza
PHAC	Public Health Agency of Canada
PHECG	Public Health Ethics Consultative Group
PPE	Personal protective equipment
RCT	Randomized controlled trial
UK	United Kingdom
US	United States
WHO	World Health Organization

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Appendix A: Overview of product characteristics and indications for use of Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b)

Table 5. Product characteristics and indications for use of Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b) as per product monograph

Product brand name and formulation	Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b)
Type of vaccine	Inactivated split-virion, egg-based vaccine
Date of authorization in Canada	• Arepanrix™ H5N1 (A/Indonesia clade 2.1.3.2): 2013-02-13 • Arepanrix™ H5N1 (A/American wigeon clade 2.3.4.4b): 2025-02-18 (marketing authorization of strain update)
Authorized ages for use	Adults and children from 6 months of age
Authorized dose and schedule	• Adults 18 years of age and above should receive 2 doses (each 0.5 mL) of Arepanrix™ H5N1 (A/American wigeon). • Children and adolescents aged 6 months to 17 years should receive 2 doses (each 0.25 mL) of Arepanrix™ H5N1 (A/American wigeon). • For all ages, the second dose should be administered at least 3 weeks (21 days) after the first dose.
Potential allergens[a]	• Trace egg protein, including ovalbumin (≤0.083 mcg per dose)[b] • Polysorbate 80 • Thimerosal
Adjuvant / Preservatives	AS03 which consists of α-tocopherol, squalene and polysorbate 80 in an oil-in-water emulsion [80].
Contraindications	As per the product monograph, history of an anaphylactic reaction (i.e., life-threatening) to any of the constituents or trace residues of the vaccine, including egg protein. See note below about NACI recommendations regarding vaccination of people who are allergic to eggs[b]
Storage	2 to 8°C
Handling	After mixing the adjuvant and antigen, the vaccine should be used within 24 hours. 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 (allow a minimum of 15 minutes) before each withdrawal.
Reconstitution	The vaccine is reconstituted by withdrawing the entire contents of the vial containing the adjuvant by means of 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

[a] Based on components listed in the product monograph that are also listed as potential allergens in the Canadian Immunization Guide. See the product monograph (available online as of December 2024) for additional components of the vaccine. for additional components of the vaccine.

[b] As per the Canadian Immunization Guide, studies have clearly demonstrated that egg-allergic persons can receive influenza vaccines. All egg-allergic individuals may be vaccinated against influenza using any of the vaccines authorized for use in Canada.

Appendix B: Summary of considerations regarding the objective of using HVAI in a non-pandemic context

Table 6. Summary of considerations regarding the objective of using HVAI in a non-pandemic context

Considerations	Summary of evidence and rationale
Preventing human infection	• Most individuals are expected to have little to no immunity to avian influenza A(H5) viruses because they have not previously circulated in humans. The limited available evidence suggests that seasonal influenza vaccines and past influenza infections will not protect against infection from the avian influenza A(H5N1) clade 2.3.4.4b strains that are currently circulating in birds and mammals. • Adjuvanted A(H5N1) HVAI have met immunogenicity criteria established for authorization of influenza vaccines. Seasonal influenza vaccines and the adjuvanted H1N1 pdm09 vaccine are authorized based on these criteria, with moderate but variable vaccine effectiveness against seasonal influenza infection reported with seasonal influenza vaccines and very good effectiveness reported with adjuvanted H1N1 pmd09 vaccines during the 2009 H1N1 pandemic. Therefore, it is plausible that HVAI that meet authorization immunogenicity criteria may also prevent human infection with avian influenza A(H5N1) viruses. However, the correlation of established immunogenicity criteria to HVAI effectiveness is unknown, and there are currently no data on the efficacy or effectiveness of HVAI against infection, clinical disease, or transmission of avian influenza A(H5N1). • For people at increased risk of exposure to avian influenza A(H5N1) through handling live virus or contact with wild or domestic birds or animals and/or their environments (Table 2), vaccination against avian influenza virus may provide another protective measure in addition to PPE and other biosecurity measures (refer to Avian influenza A(H5N1): Prevention and risks and Guidance on human health issues related to avian influenza in Canada [HHAI]).
Preventing severe disease	• The spectrum of clinical disease caused by the currently circulating avian influenza A(H5N1) clade 2.3.4.4b viruses across different ages and population groups is currently uncertain. • There have been a limited number of cases in the US, most of which have occurred in farm workers and almost all of which have been mild at the time of NACI deliberations. However, the spectrum of illness is not yet fully understood. Even if only a small proportion of cases are severe, an increase in the overall number of cases would be expected to lead to an increase in severe cases. • At the time of NACI deliberations, the first (and then only) severe human case of avian influenza A(H5N1) clade 2.3.4.4b in North America occurred in a teenager in BC. Globally, previous avian influenza A(H5N1) strains have resulted in severe disease in humans with a CFR of approximately 50%. • Based on the effectiveness against severe disease of seasonal influenza vaccines and adjuvanted A(H1N1) pdm09 vaccines assessed against immunogenicity criteria for authorization, it is plausible that authorized HVAI could provide protection against severe disease.
Limiting opportunities for viral adaptations	• Preventing human infection and spillback (i.e., transmission of virus from humans to animals) with avian influenza A(H5N1) could potentially limit opportunities for genetic changes through mutations or reassortment between

	influenza virus strains that could result in the virus acquiring the ability to cause human-to-human transmission. • Attempting to prevent transmission from animals to humans in Canada should weigh the benefits and risks to the individual and may have limited impact on preventing human-to-human transmission or a possible future pandemic without a concerted global effort.

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