

Protective measures and human antibody response during an avian influenza H7N3 outbreak in poultry in British Columbia, Canada

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ABSTRACT

Background: In 2004 an outbreak of avian influenza of the H7N3 subtype occurred among poultry in British Columbia, Canada. We report compliance with recommended protective measures and associated human infections during this outbreak.

Methods: We sought voluntary participation by anyone (cullers, farmers and their families) involved in efforts to control the poultry outbreak. Recruitment was by advertisements at the worker deployment site, in local media and through newsletters sent directly to farmers. Sera were tested for antibody to H7N3 by microneutralization assay. A subset of 16 sera (including convalescent sera from 2 unprotected workers with conjunctivitis from whom virus had been isolated) was further tested by Western blot and routine and modified hemagglutination inhibition assays.

Results: A total of 167 people (20% to 25% of all workers) participated between May 7 and July 26, 2004. Of these, 19 had experienced influenza-like illness and 21 had experienced red or watery eyes. There was no significant association between illness reports and exposure to infected birds. Among 65 people who entered barns with infected birds, 55 (85%) had received influenza vaccine, 48 (74%) had received oseltamivir, and 55 (85%), 54 (83%) and 36 (55%) reported always wearing gloves, mask or goggles, respectively. Antibody to the H7 subtype was not detected in any sera.

Interpretation: During the BC outbreak, compliance with recommended protective measures, especially goggles, was incomplete. Multiple back-up precautions, including oseltamivir prophylaxis, may prevent human infections and should be readily accessible and consistently used by those involved in the control of future outbreaks of avian influenza in poultry. Localized human avian influenza infections may not result in serologic response despite confirmed viral detection and culture.

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Human infection due to avian influenza is a concern because of the potential for pandemic candidates to emerge either directly through adaptive mutation or indirectly through genetic reassortment with human

influenza viruses.¹ Global anxiety is increasing because of expanding poultry outbreaks and human infections due to the Eurasian H5N1 subtype of avian influenza, with predictions of its entry into North America via migratory flyways, international trade in fowl or contaminated fomites. Less attention has been paid to other avian influenza subtypes that have also caused poultry outbreaks and human infections.

Between 1959 and 2002, 11 poultry outbreaks of highly pathogenic avian influenza of the H7 subtype were reported worldwide, primarily H7N7 and H7N3 strains.¹⁻³ Designation of avian influenza as having high or low pathogenicity refers to virulence in poultry; potential transmissibility or virulence in humans cannot be extrapolated from these designations. Humans have not been considered at high risk of infection with H7 subtypes, although isolated cases of H7N7 conjunctivitis have been reported.⁴⁻⁷ Systemic antibody response has not been consistently detected in human cases.⁸⁻¹⁰

Between Feb. 28 and May 7, 2003, an extensive outbreak of highly pathogenic avian influenza of the H7N7 subtype occurred among poultry in the Netherlands.¹¹⁻¹³ After infection was confirmed in 19 people, all poultry workers were required to receive influenza vaccine (to reduce the risk of human influenza and genetic reassortment with avian influenza) and oseltamivir prophylaxis (to reduce replication of the avian influenza virus and illness in exposed people) and were also required to wear personal protective equipment (PPE).¹² Ultimately, 89 human H7N7 infections were confirmed, consisting primarily of conjunctivitis but also including the death of a previously healthy veterinarian in whom the virus had changed.^{12,14} Antibody to the H7 subtype could not be found in the sera of exposed people by routine hemagglutination inhibition assay but was detected in half of 500 people tested by a modified hemagglutination inhibition approach.^{13,15-17}

Between Feb. 17 and May 18, 2004, an outbreak of avian influenza due to an H7N3 subtype occurred among poultry in the Fraser Valley of British Columbia, Canada. The source of the virus was never determined. Within days, the virus causing this outbreak had converted from low to high pathogenicity on the index farm.¹⁸ Ultimately, 42 commercial farms and 11 backyard flocks, comprising 1.3 million birds, were considered infected (Fig. 1).¹⁹⁻²³ Most infected commercial flocks (34/42 or 81%) were identified between Mar. 21 and Apr. 24. Infected flocks, as well as non-infected birds from an addi-

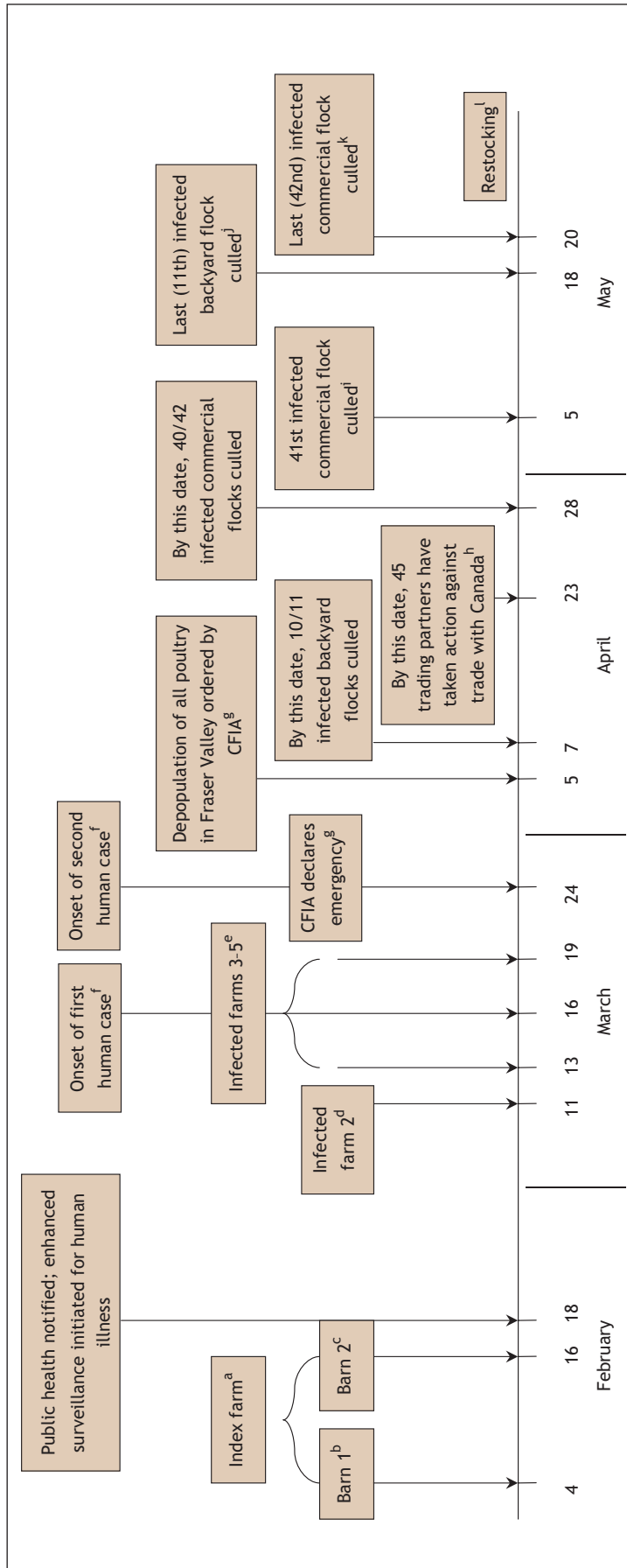


Fig. 1: Chronology of the 2004 outbreak of avian influenza H7N3 in the Fraser Valley, British Columbia.¹⁸⁻²³

^aIndex farm included an older flock and a younger flock housed in 2 separate barns.

^bOn Feb. 4, the older flock in barn 1 of the index farm had reduced egg production and slightly increased mortality rate (to 0.5% over 72 h) that subsequently resolved. The virus was later identified (on Feb. 19) as low-pathogenicity avian influenza H7N3 (intravenous pathogenicity index [IVPI] = 0).

^cOn Feb. 16, the younger flock in barn 2 of the index farm had a sudden increase in mortality (to more than 25% in 48 h). Birds on the index farm were destroyed and quarantine was imposed on Feb. 20 to attempt containment. Virus from birds in barn 2 was later characterized (on Mar. 8) as high-pathogenicity avian influenza H7N3 (IVPI = 2.96). Conversion from low pathogenicity to high pathogenicity was attributed to recombination between hemagglutinin and matrix genes.^{18,19}

^dEfforts at containment had failed: a second farm (located several kilometres from the index farm) was found to be infected with high-pathogenicity avian influenza H7N3.

^eThe Canadian Food Inspection Agency (CFIA) officially notified the Office International des Epizooties of the outbreak of high-pathogenicity avian influenza on Mar. 13. The United States closed its border to BC poultry and poultry products.

^fOnset of unilateral conjunctivitis in unprotected workers following direct conjunctival contact with infected birds during culling on Mar. 13 (case 1, farm 2) and Mar. 22-23 (case 2, farm 3). Virus isolated from the nose of case 1 was low-pathogenicity H7N3 and from the conjunctiva of case 2 was high-pathogenicity H7N3.

^gBy Apr. 5, 20 commercial flocks were infected. Pre-emptive depopulation of all poultry in the Fraser Valley was announced by the CFIA. Most infected commercial flocks (34/42 or 81%) were detected between Mar. 21 and Apr. 24, 2004.²¹

^hBy Apr. 23, a total of 45 trading partners had taken action against Canada: 29 against all of Canada, 16 against live poultry and poultry products from British Columbia.

ⁱA commercial duck farm without signs of infection was identified pre-slaughter as being infected with low-pathogenicity H7N3.

^jIn total, 11 backyard flocks were deemed infected; the last was detected and culled on May 18.

^kIn total, 42 commercial flocks were deemed infected; the last was detected on May 18 and culled on May 20.

^lAfter the events depicted in this chronology, the CFIA declared all depopulated premises eligible for restocking on July 9, the United States lifted trade restrictions on Aug. 17, and the European Union lifted restrictions on Oct. 1.

tional 410 commercial farms (14.9 million birds) and 553 backyard flocks (18 000 birds) were destroyed in an effort to halt circulation of the virus by culling the primary susceptible host sustaining its replication (poultry). Economic losses were estimated at more than \$300 million.²³

The BC Centre for Disease Control (BCCDC) was notified of the Fraser Valley outbreak on Feb. 18, 2004.²¹ Enhanced surveillance for conjunctivitis and influenza-like illness was implemented, and the protective measures that were recommended were based on the Dutch experience (Fig. 1).²¹ On Mar. 16 and Mar. 24, 2 workers experienced onset of mild unilateral conjunctivitis (the first accompanied by coryza, the second by headache) following separate incidents of direct conjunctival contact with infected poultry during culling operations on Mar. 13 and Mar. 22–23, respectively. Neither worker had followed recommended precautions. Influenza was isolated from a nasal specimen collected 3 days after exposure from the first worker (low-pathogenicity H7N3) and from a conjunctival sample collected 1–2 days after exposure from the second (high-pathogenicity H7N3).

Following these reports, protective measures were enhanced. The Canadian Food Inspection Agency (CFIA) provided fit-tested respirators, gloves, goggles and protective clothing for its workers. The BCCDC developed fact sheets to explain the risks and the rationale for the precautions and provided free influenza vaccine and oseltamivir (75 mg once daily during exposure and for 1 week thereafter) to both farmers and CFIA workers.

We report here the results of a sero-survey to assess compliance with recommended protective measures and to identify unrecognized human infections during this large poultry outbreak.

Methods

We sought voluntary participation from anyone involved in any aspect of outbreak control. Recruitment was by advertisements posted at the worker deployment site, published through the media and distributed by the poultry association in newsletters sent directly to farmers. The advertisements invited anyone involved in control of the outbreak to participate in a study being conducted by the BCCDC to test for possible human infections and provided information on how to enroll. To enable comparison of serologic results across risk categories, we accepted participation by CFIA workers, farmers and their family members with and without direct contact with poultry, infected poultry or other poultry workers since February 2004. A mobile trailer at worker locations served as the study clinic. Blood samples (7 mL each) and interview data were collected by trained nurses using a standard questionnaire. Epidemiologic data were collected to describe the study cohort, to evaluate compliance with recommended protective measures and to aid in the interpretation of serologic results; these data included baseline characteristics (age, sex, province of residence, occupation), history of possible exposure to avian influenza (poultry-related activities before and during the 2004 outbreak, direct contact with infected or non-infected birds or other workers, number of birds or farms visited), protective meas-

ures applied and consistency of their use (categorized as never, sometimes or always), and illness experience between February 2004 and the date of blood collection and within 48 hours of starting oseltamivir among those who received this drug. Direct contact was defined as handling poultry or poultry products or sharing the same confined airspace. Influenza-like illness was defined as fever and one or more of cough, rhinorrhea, sore throat, myalgia or headache.¹² Univariate statistical comparisons were performed by χ^2 test. The Ethics Board of the University of British Columbia granted approval.

All sera were tested for antibody by microneutralization assay.^{24,25} A subset of 16 sera was also tested by Western blot and by routine and modified hemagglutination inhibition.¹⁵ This subset consisted of sera from 10 participants randomly selected from the full list of participants and from an additional 6 participants who were known to have had unprotected exposure to infected birds. The latter group included the 2 participants from whom virus had been isolated and from whom convalescent serum was collected more than 21 days after onset of symptoms.

Microneutralization assay was performed as previously described²⁴ using the H7N3 human isolate from British Columbia (A/Canada/444/04). Animal control serum against A/H7N3/Turkey/Minnesota/29206/83 was provided by Dr. J. Pasick, CFIA, Winnipeg. Neutralizing titer for positive control was 1:320 and for negative sera less than 1:8. Western blot was performed as previously described by Bastien and associates.²⁶ Recombinant hemagglutinin protein was generated by infecting insect cells with recombinant baculovirus carrying the H7 gene from A/Canada/444/04. Routine hemagglutination inhibition assay with turkey erythrocytes and modified hemagglutination inhibition assay with horse erythrocytes were performed as previously described.^{15,17,24,25}

Results

Baseline characteristics

There were 167 participants, of whom 37 were commercial or backyard farmers, farm workers or their family members; the rest were CFIA staff or hired general labourers, including 13 veterinarians and other workers (20% to 25% of the staff who had been involved in outbreak control).²⁰ Most participants (155 or 93%) lived in British Columbia; the other participants were residents of other provinces (6 from Ontario, 3 from Nova Scotia, and 1 each from Saskatchewan, Quebec and Newfoundland), reflecting the recruitment of workers from across Canada to assist in control efforts. Sera were collected between May 7 and July 26, 2004. Of the 167 participants, 111 (66%) reported direct contact with any poultry as part of outbreak control activities, and 91 (54%) reported direct contact with infected birds since February 2004. The remaining participants, including support staff and occupational health and security personnel, had had no direct contact with poultry but had been exposed to others who had. No participants reported contact with infected birds before February 2004. The percentage of people reporting exposure to more than 100 birds overall was greater among those who had had di-

rect contact with infected birds than among those who had had contact only with non-infected birds (50/91 [55%] v. 2/20 [10%]; $p < 0.001$). Of the 91 participants who reported direct contact with infected birds, the median number of infected farms visited was 5 (min-max: 1-42). All but 4 of the study participants had been involved in outbreak-related activities for more than 2 weeks. For all but 2 of the 91 participants who reported direct contact with infected birds, the interval between the last exposure and participation in the survey was more than 2 weeks (9 days each for the remaining 2).

Prophylaxis and personal protective equipment

Thirty-five participants (21%) reported having been vaccinated that season before February 2004 and were not re-vaccinated. This rate is consistent with influenza immunization coverage in the general population of British Columbia (27%).²⁷ Participants with direct contact with infected poultry were more likely to report having been vaccinated than those without direct contact (76/90 [84%] v. 30/74 [41%]; odds ratio [OR] 8.0; 95% confidence interval [CI] 3.6-17.8). Oseltamivir use was also greater among those who had direct contact with infected poultry (64/90 [71%] v. 10/75 [13%]; OR 16.0; 95% CI 6.7-39.2) (Table 1). Duration of oseltamivir use was less than 7 days for 12 participants (16%), 7-13 days for 13 (18%), 14-27 days for 34 (47%), 4-6 weeks for 13 (18%) and more than 6 weeks for 1 (1%). The 11 farmers who reported direct contact with infected birds reported rates of vaccination (8 [73%]) and antiviral use (7 [64%]) that were comparable, if slightly lower than, the corresponding rates for the 28 workers involved in euthanizing poultry (22 [79%] for both rates).

Use of PPE during select poultry-related activities is shown in Table 2. Among the 65 people who reported entering a barn with infected birds, 55 (85%) had been vaccinated, 48 (74%) took oseltamivir, and 55 (85%) and 54 (83%) always wore gloves and masks respectively, but only 36 (55%) wore goggles at all times. Among the 29 people in this group who reported that they did not wear goggles at all times, 22 (76%)

took oseltamivir. The use of PPE was less consistently reported by farmers for times of exposure to infected birds than by workers for specific culling-related activities involving infected birds (Table 2).

Symptoms

A larger percentage of those with direct contact with infected poultry than of those with exposure only to non-infected poultry reported red or watery eyes (16/90 [18%] v. 1/20 [5%]; $p > 0.05$), but this symptom was not associated with eye discharge (Table 3). Eighteen survey participants with conjunctivitis- or influenza-like illness were previously identified as meeting a suspect case definition for avian influenza during the outbreak.²¹ These participants provided nasal and/or conjunctival specimens in addition to sera; virus was not detected in any other than the 2 previously mentioned cases.²¹

Of the 25 participants with red or watery eyes or eye discharge (or both), 14 (56%) had had direct contact with infected poultry; of these, 12 (86%) had taken oseltamivir and 12 (86%), 11 (79%) and 9 (64%) had always worn a mask, gloves or goggles, respectively. Among the 5 who had not always worn goggles, 3 took oseltamivir at all times.

Adverse events in association with oseltamivir typically occur with the first dose.²⁸⁻³² Therefore, symptoms beginning within 48 hours of initiation of oseltamivir were specifically solicited. Consistent with previous investigations, oseltamivir was well tolerated by the 75 participants reporting its use. Gastrointestinal symptoms were most often reported: 10 participants (13% of those taking the drug) reported nausea, 9 (12%) stomach pain and 4 (5%) diarrhea. In addition, 4 participants (5%) reported headache. No other symptom was reported by more than 5% of participants.

Antibody detection

Antibody to the H7 subtype could not be detected in any sera by the microneutralization assay. Sera additionally tested by

Table 1: Baseline characteristics of survey participants

Characteristic	Group; no. (%) of participants*	
	All participants <i>n</i> = 167	Participants with direct contact† with known infected birds <i>n</i> = 91
Median age (min-max), yr	34 (0-73)	33 (16-67)
Male sex	88 (53)	59 (65)
Received influenza vaccine	107‡ (65)	76‡ (84)
Received oseltamivir	75‡ (45)	64 (70)
For treatment§	4‡ (5)	4‡ (6)
For prevention§	70‡ (95)	58‡ (94)
Took oseltamivir every day while in contact with poultry	44‡ (27)	40‡ (44)

*Except where indicated otherwise.

†Same confined airspace or handling poultry or poultry products of infected birds.

‡Information missing for 1-5 participants; percentages based on number of participants for whom information was available.

§Percentages based on number of participants who received the drug.

Western blot and routine and modified hemagglutination inhibition also yielded negative results, including the convalescent sera collected at days 34 and 22 after onset of symptoms from the 2 participants with conjunctivitis from whom virus had earlier been isolated.

Interpretation

The BC outbreak in 2004 was the largest poultry outbreak of avian influenza recorded in Canada and the first in this country due to an H7N3 subtype.³³ The virus evolved rapidly from low pathogenicity to high pathogenicity on the first affected

farm. This was also the first outbreak worldwide in which it was confirmed, through virus isolation, that H7N3 avian subtypes, both high and low pathogenicity, can cause human infection and illness.^{34,35}

Once introduced, avian influenza viruses flourish in the setting of highly susceptible and genetically monotonous populations of poultry housed by the tens of thousands in commercial barns. Accelerated evolution of the virus in such settings is thought to occur through abundant error-prone replication, facilitating, through the sheer number of mutating viruses, the chance emergence of variants with altered characteristics. Pandemics of the previous century are

Table 2: Use of barrier precautions during selected poultry-related activities performed by participants

Occupation or activity*	n	No. (%) with direct contact† with known infected birds	No. (%) using barrier precautions at all times during direct contact† with known infected birds		
			Gloves	Mask	Goggles
Commercial farmer	29	11/29 (38)	5/11 (45)	6/11 (54)	3/11 (27)
Veterinarian	13	5/13 (38)	5/5 (100)	4/5 (80)	4/5 (80)
Collecting specimens	10	10/10 (100)	10/10 (100)	9/10 (90)	7/10 (70)
Cleaning equipment	47	32/47 (68)	21/32 (66)	19/32 (59)	13/32 (41)
Catching birds	56	37/56 (66)	30/37 (81)	29/37 (78)	17/37 (46)
Euthanizing birds	38	28/38 (74)	25/28 (89)	24/28 (86)	18/28 (64)
Transporting dead birds	31	25/31 (81)	22/25 (88)	20/25 (80)	13/25 (52)
Incinerating dead birds	7	5/7 (71)	4/5 (80)	4/5 (80)	3/5 (60)
Composting dead birds	44	31/44 (70)	26/31 (84)	25/31 (81)	12/31 (39)
Present in poultry barn for any reason	88	65/88 (74)	55/65 (85)	54/65 (83)	36/65 (55)

*Not mutually exclusive.

†Same confined airspace or handling poultry or poultry products of infected birds.

Table 3: Symptoms experienced between February 2004 and survey enrollment

Symptom	No. (%) of participants			
	All participants n = 167	No contact with any poultry n = 56	Direct contact with non- infected poultry only n = 20	Direct contact* with infected poultry n = 91
Feverishness	20† (12)	4 (7)	3 (15)	13‡ (15)
Temperature > 37.8°C	5† (3)	3 (5)	0 (0)	2‡ (2)
Cough	41† (26)	11 (20)	6 (30)	24‡ (28)
Sore throat	41† (25)	14 (25)	6 (30)	21‡ (24)
Runny nose	46† (28)	14 (25)	7 (35)	25‡ (28)
Headache	23‡ (14)	6 (11)	2 (10)	15‡ (17)
Body aches	23† (14)	6 (11)	5 (25)	12‡ (14)
Red or watery eyes	21† (13)	4 (7)	1 (5)	16‡ (18)
Eye discharge	9† (6)	3 (5)	2 (10)	4‡ (5)
Diarrhea	12‡ (7)	4 (7)	1 (5)	7‡ (8)
Influenza-like illness§	19† (12)	4 (7)	3 (15)	12† (14)

*Same confined airspace or handling poultry or poultry products.

†Information missing for 6-10 participants; percentages based on number of participants for whom information was available.

‡Information missing for 1-5 participants; percentages based on number of participants for whom information was available.

§Defined by Koopmans and colleagues¹² as report of fever and one or more of cough, rhinorrhea, sore throat, myalgia or headache.

thought to have evolved not from highly pathogenic avian influenza, but from low-pathogenicity forms that adapted surreptitiously to humans either directly (in the pandemic of 1918) or indirectly through genetic reassortment (in the pandemics of 1957 and 1968).^{36,37} In this context, all avian influenza viruses in domestic poultry may have presumed pandemic potential.³⁶⁻³⁸ Exposed farmers and cullers constitute a potential interface between novel avian influenza viruses and the communities to which the workers return. To prevent further spread between barns and to protect individual workers and their communities from a highly changeable virus, rigorous attention to biosecurity and to occupational and public health measures is important during all outbreaks of avian influenza in commercial poultry.

Participants in this survey were asked to describe any concerns they had about biosafety or personal risk while working on the outbreak; they most often cited concerns related to eye protection, including feathers and sawdust in the air, poor fit of goggles over regular glasses, frequent fogging and general interference with vision. Given that the only human infections in British Columbia followed direct contact with unprotected conjunctiva, these concerns should be addressed. Other investigators have also underscored the importance of eye protection and the particular ocular tropism of H7 subtypes.^{12-14,39,40} Human influenza viruses are thought to bond preferentially to $\alpha 2,6$ cellular receptors, which predominate in the upper respiratory tract.^{39,40} Conversely, avian influenza viruses preferentially bond to $\alpha 2,3$ receptors, which are expressed with preponderance in the human eye and deep in the lung.^{39,40} Avian influenza viruses that successfully replicate in the conjunctiva may gain access to the respiratory tract through the nasolacrimal duct. Given enough opportunities, adaptation to $\alpha 2,6$ receptors in the upper airway may occur, setting the stage for efficient human-to-human transmission.⁴⁰ A combination of oseltamivir and PPE, including goggles, may be warranted as back-up precautions to guard against this possibility, since compliance with any one protective measure, notably PPE, appears to be unreliable.

Among participants in our survey, a greater percentage of those who had direct contact with infected birds than of those without such exposure reported red or watery eyes. These ocular symptoms were not accompanied by discharge. Those who reported exposure to infected birds also reported exposure to more birds overall, which would have increased opportunities for eye irritation. Most of those who reported eye symptoms received oseltamivir prophylaxis and would not have been considered at high risk of infection with avian influenza virus. Enhanced surveillance confirmed 2 cases of H7N3 conjunctivitis in unprotected workers with symptom onset and virus isolation several days after exposure. These findings, delayed by a compatible incubation period, are unlikely to have been the result of irritation, trauma or contamination. Lack of serologic response in these confirmed cases may raise doubts about the sensitivity of our assay. Microneutralization is the definitive method for antibody detection.²⁴ It is possible that mild infections induced by H7 viruses, especially those involving the immunoprivileged eye, may not in-

duce a strong systemic antibody response.⁸⁻¹⁰ In the Netherlands, routine hemagglutination inhibition failed to detect antibody to H7N7, but modified hemagglutination inhibition identified an unprecedented number of subclinical infections. These, however, were not confirmed by microneutralization assay.^{13,15-17} We performed multiple retrospective assays, including modified hemagglutination inhibition, without further yield. Given the uncertainties in serologic assays for avian influenza, caution should be applied in the interpretation of serologic results. Definitive evidence for human infection is the real-time detection and isolation of virus, particularly from sites where symptoms are manifest.

Management of the BC outbreak benefited from prior experience in the Netherlands. Compliance with vaccination and prophylaxis was comparable, but reported compliance with PPE was generally higher among BC participants than among those surveyed in the Netherlands.¹³ In British Columbia, vaccine and antiviral drugs were supplied free of charge to both farmers and cullers hired by the CFIA. Since 2004, influenza vaccine has been provided free annually to residents of British Columbia who work with live poultry and/or swine. During the BC outbreak, the CFIA provided PPE to its workers, but a mechanism for providing PPE to farmers was not established. Our survey results may reflect the resulting differential in the use of barrier precautions. Reduced use of barrier precautions by farmers in particular was also noted during the outbreak in the Netherlands.¹³ Surveys conducted in both British Columbia and the Netherlands were voluntary, were based on self-reporting and recall, and included only a limited number of those involved in controlling the outbreak. Participants were engaged in multiple outbreak-related activities, so it was not possible to exclusively distinguish them on that basis. Unlike vaccine or antiviral use, PPE must be repeatedly donned and doffed, and compliance associated with each activity might be more difficult to recall or report. Given the extent of the outbreak and the number of short-term workers involved, the true denominator of those potentially exposed was difficult to quantify; associated biases should be kept in mind. Nonetheless, lessons from both British Columbia and the Netherlands are clear: recommended protective measures should be provided and readily accessible to any potentially exposed person during future outbreaks of avian influenza. These precautions should be simple and feasible and should enable safe and unobstructed work; evaluation of compliance, effectiveness and impact should be undertaken. Given predictions of the further inexorable spread of the Eurasian H5N1 virus and its possible entry into North America, these lessons should be collectively addressed now.

This article has been peer reviewed.

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