

# Avian Influenza: Recent Epidemiology, Travel-Related Risk, and Management

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**Abstract** H5N1 influenza continues to smolder in Southeast Asia over the past 5 years, but the emergence of H7N9 in China in 2012 raised concerns for a new avian influenza threat. In contrast with H5N1 with over 650 confirmed cases over 11 years, H7N9 has infected over 450 persons within 2 years. The case fatality rate for H7N9 (35 %) is lower than for H5N1 (60 %) or H10N8 (67 %) but is comparable to that for the Middle East respiratory syndrome coronavirus (MERS CoV), another emerging zoonosis with travel-associated importations. Exposure to poultry and fomites are considered the likely sources of infection for H7N9, H5N1, and H10N8, with limited human-to-human transmission in close contacts. Most cases have occurred in local populations of affected countries, and travel-related risk can be mitigated by avoiding exposure. Vaccines, antivirals, and other therapeutics remain in development stage or of modest benefit for dangerous infections carrying high morbidity and mortality.

**Keywords** Avian influenza · H5N1 · H7N9 · Influenza · Travel · Therapy · Epidemiology · Emerging infections · Zoonoses

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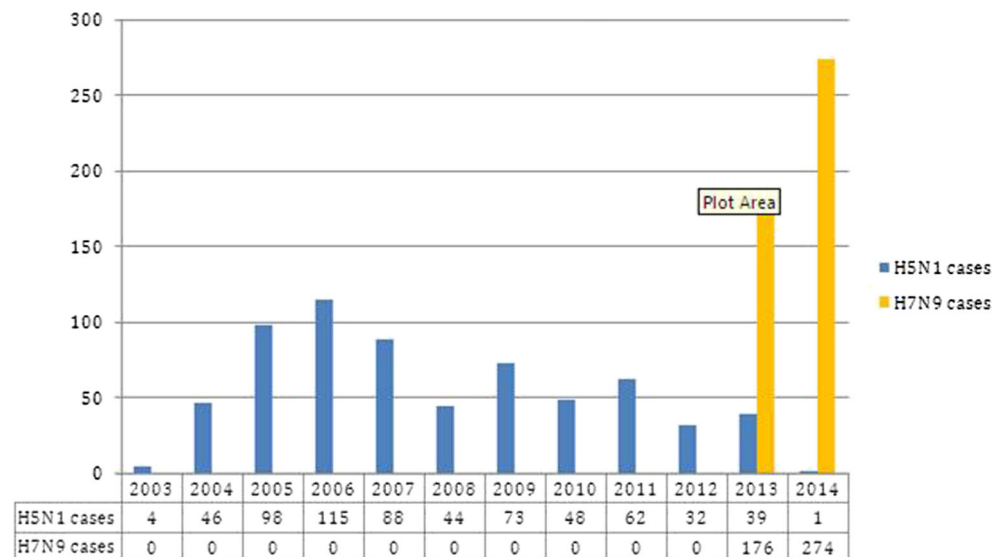
## Introduction

For decades, influenza A has been on the watch list as a potential pandemic pathogen. In the past 15 years, two avian influenza strains, H5N1 and H7N9, have successfully jumped the species barrier, resulting in outbreaks of human infection. Although there has been no evidence of sustained human-to-human transmission to date, if this occurs, we would be closer to fulfilling all the necessary conditions for a devastating human pandemic. H5N1 influenza continues to smolder in Southeast Asia since 1997 [1], but the emergence of H7N9 in China in 2013 raised concerns for a new avian influenza threat [2]. In contrast with H5N1 with 650 confirmed cases since 2003, H7N9 has infected over 400 persons in just over 1 year [3, 4]. How this situation evolves over the next few seasons may have far-reaching implications for our cumulative pandemic risk globally (Fig. 1).

## Epidemiology

The H5N1 virus was first isolated from a farmed goose in the Guangdong Province of China in 1996, with the first human cases reported a year later in Hong Kong [5]. After this first cluster of 18 cases, H5N1 reemerged in 2003 in China. Subsequently, H5N1 spread through Southeast Asia. Turkey marked the first occurrence outside of Asia, followed by Iraq, Azerbaijan, and Egypt between January and April 2006 [1]. A total of 650 laboratory-confirmed human infections have been officially reported to the World Health Organization (WHO) from 15 countries in Asia, Africa, the Middle East, and Europe [3]. Sporadic importations have occurred rarely, most recently in Canada from a traveler returning from Beijing [6]. H5N1 cases peaked in January 2006, when the outbreak was brought under control through expensive culling campaigns in affected countries like Thailand, Vietnam, and Indonesia. Yearly peaks

**Fig. 1** H5N1 and H7N9 human cases, 2003–2014



around January have continued since then, but these have gradually stabilized [3].

In the aftermath of SARS, China established a national surveillance system to detect novel pathogens using cases of pneumonia of unknown etiology (PUE) as beacons. Health care facilities in China are mandated to report details to local public health officials of all patients who have fever  $>38^{\circ}\text{C}$ , radiographic features of pneumonia, low or normal leukocyte count, and no response or deterioration after 3 to 5 days of standard antimicrobial therapy. In such cases, respiratory tract specimens are tested for influenza H5N1 and for SARS coronavirus. Clusters, defined as two or more cases of PUE with an epidemiological link that cannot be explained by local investigators, are escalated to the national Centers for Disease Control (CDC) for further investigation [7]. In March 2013, a case of PUE was tested for new influenza subtypes; this became the first documented case of H7N9 and led to the first three cases being diagnosed in Shanghai and Anhui, although no epidemiological link was established between the three cases [8]. After these cases were described, the definition of PUE was broadened and more discretion given to individual physicians to test when clinically appropriate in order to increase the sensitivity of the program.

By December 2013, 139 cases of H7N9 had been confirmed, and reporting continued until May 2013 [4]. This outbreak resurged in December 2013, peaking around the Chinese New Year celebration in February 2014. Sixty-eight percent of individuals with H7N9 identified through the PUE surveillance system were from the Shanghai municipality and Zhejiang Province. These two regions, however, only contain about 6 % of the total Chinese population; conversely, 10 % of H7N9 cases were reported from the remaining 21 provinces where approximately 57 % of the populations reside. These numbers may represent concentrated foci of infection; however, variable reporting among regions may yield inaccurate

estimates of the true disease burden and distribution. Such data may provide a false and potentially dangerous reassurance to travelers [7].

PUE surveillance only provides numbers of ill cases admitted to a hospital. To establish the true spectrum of clinical cases, a sentinel survey was conducted among 541 outpatient clinics and emergency departments spread across 31 provinces. This yielded 5 of the total 130 lab-confirmed cases by May 27 2013. Three of the cases were in young children; four had exposure to live animals. Three had mild to moderate illness while two were admitted to a hospital, one with pneumonia; subsequently, all recovered [9].

Seroepidemiology investigations have been conducted to determine the extent of virus circulation and spectrum of disease. Most studies use standard hemagglutinin inhibition assays or microneutralization assays according to WHO criteria [10]. A meta-analysis of H5N1 studies which included seroepidemiology studies that met WHO criteria and excluded diagnosed H5N1 cases found a seroprevalence of 1.2 % (95 % CI 0.6 to 2.1) in 7304 participants, with higher seropositivity (1.4 %) in poultry workers [11]. Given the higher H5N1 seropositivity rate among poultry workers, this occupational group would likely have a higher risk of early exposure to emerging avian influenza viruses. A retrospective study using stored serum samples from 1544 occupational groups including workers in live poultry markets, farms, slaughterhouses, and wild bird habitats in eastern China (Shanghai, Zhejiang, Jiangsu, and Anhui) was analyzed to look for evidence of circulating H7N9 prior to the onset of the outbreak. Surprisingly, samples taken between January and November 2012 showed no evidence of immune reactivity to H7N9 [12].

H5N1 human infections have occurred mostly in young persons, with children under age 12 years comprising 50 % of the 1997 outbreak cases [13]. By contrast, H7N9 infections have affected predominantly older men. In the first large series

of 139 laboratory-confirmed H7N9 cases, 71 % were male with a median age of 60 and 73 % lived in urban areas, while those who were diagnosed as part of the outpatient sentinel survey who tended to have less severe disease were predominantly children [9, 14]. Several investigators have explained this finding as reflecting social patterns: grandfathers are exposed shopping at live poultry markets, while grandmothers stay at home and younger adults are at work.

The evidence for avian-to-human transmission comes from epidemiological and molecular investigations. Among the first 139 H7N9 cases, 82 % reported a history of exposure to live animals including chickens [14]. Similarly, a case-control study of the first 15 H5N1 cases demonstrated that 64 % of cases compared to 29 % of controls had visited live poultry markets. However, eating or preparing poultry products was not a risk factor [15]. Another case-control study of 25 H7N9 cases with 93 matched controls found that direct exposure to poultry in the 2 weeks prior to illness onset was a risk factor for acquiring infection [16].

Although transmission is predominantly after poultry contact, limited human-to-human transmission is possible. In the first H7N9 outbreak, four household clusters were reported, yet in three of these households, only the index case had exposure to poultry. Infected household members had prolonged close contact to the index cases [14]. Similarly for H5N1, investigations indicate at least three clusters with a likely human-to-human transmission in Thailand and Indonesia [17, 18]. Transmission is not efficient; in one study, throat swabs were collected from symptomatic contacts, and paired sera from asymptomatic contacts showed no evidence of infection. Spread may occur outside households, if there is close contact. Seroepidemiology studies showed seropositivity in 1 out of 26 in a tour group, and exposed health care workers had 3.7 % seropositivity compared to 0.7 % among unexposed health care workers [18]. As the number of older travelers increase, with their propensity for tour groups, this may become an important consideration [19].

The most recent avian influenza jumping the species barrier into humans is H10N8. In November 2013, a 74-year-old woman visited a live poultry market 4 days before becoming ill; she died 9 days later. Genetic analysis confirmed that all viral genes were of avian origin, prompting speculation whether this could start the next epidemic. There was concern that H10N8 could be even more widespread than H7N9 because H10N8 has primarily been found in migratory birds, rather than poultry. Thankfully, only two cases have officially been reported to date (Table 1) [20].

## Virology

Influenza viruses belong to the orthomyxovirus family, with human infections caused by both influenza A and B. Novel

subtypes result from the reassortment of gene segments when two viruses are circulating in a single host. Phylogenetic analysis has indicated that H5N1 is a reassortment of at least four viruses, including goose H5N1 hemagglutinin and teal H6N1 neuraminidase, with internal genes from both quail H9N2 and teal H6N1 [21].

Avian sampling data suggests that the H7 component of the current H7N9 human outbreak comes from the H7N3 domestic duck virus in China, while the closest N9 probably originated from wild birds in South Korea. Screening of virus archives with subsequent computation of the evolutionary pathways indicates that reassortments have happened on at least two independent occasions, firstly, H7 with H9N2 to generate H7N2 followed by a second reassortment event with bird H7N9 [22].

The current low transmissibility of H5N1 and H7N9 is believed to be related to the site at which the avian influenza viruses bind to human respiratory tract. Influenza viruses bind with sialic acid receptors of which there are two subtypes relevant for avian influenza strains:  $\alpha$ -2,3 sialic acid receptors found in the gastrointestinal tract of birds and also in the lower respiratory tract of humans and  $\alpha$ -2,6 sialic acid receptors which are found in abundance in the human upper respiratory tract. Influenza viruses adapted to avian hosts selectively bind to  $\alpha$ -2,3 sialic acid receptors, whereas those adapted to humans bind to the  $\alpha$ -2,6 subtype. Genetic sequencing of binding sites and X-ray crystallography reveal that H7N9 binds strongly to  $\alpha$ -2,3 receptors and weakly to  $\alpha$ -2,6, unlike pandemic H1N1 which preferentially binds to  $\alpha$ -2,6 receptors [23, 24]. Although H7N9 and H5N1 are poorly adapted for human transmissibility at the present time, changes in receptor binding may occur with accumulated mutations arising from host pressure and faulty viral RNA replication. Some of the necessary mutations have already been identified in H5N1; passage through ferrets has produced isolates capable of preferential binding to  $\alpha$ -2,6 receptors, making this situation theoretically possible [25].

## Clinical Features

### Presenting Features

Case series are useful in reporting clinical features of avian influenza. However, these have the inherent limitation of small series and may not describe the full spectrum of disease. For H7N9, there is a detailed description of 113 out of 132 of the first reported cases [26]. The largest H5N1 report contains information for 79 cases in 5 different countries over a period of 8 years, with variable amounts of information from each country's dataset [27, 28].

Fever and cough were described in all the H7N9 cases, whereas one case of H5N1 did not have fever, 67 to 100 % had cough, and 3 H5N1 cases had no respiratory symptoms at

**Table 1** Epidemiology and travel-related risk

	H5N1	H7N9	H10N8
First reported human cases	1997	2012	2013
Global case count (total)	650	407	3
Global case fatality (total)	386	158	2
Case fatality rate (%)	59	39	67
Data up to date as of	May 5, 2014	April 5, 2014	January 30, 2014
Number of cases in 2014	1	257	2
Number of cases in 2013	39	150	1
Number of cases in 2012	32	0	0
Age (years), median	14	61	N/A
Age (years), range	3–88	1–58	55–73
Gender (% female)	31	57	100
Poultry exposure (%)	55.9	83	100
Top 3 countries in 2013 (cases)	Cambodia (26) Egypt (4) Indonesia (3)	China	China
Travel-related cases (2013–2014)	Canada (1)	Hong Kong (10) Taiwan (4) Malaysia (1)	None reported

all. Sore throat and rhinorrhea are reported for H5N1 but is not mentioned in H7N9 reports, while dyspnea was present in most cases of H7N9 (62 %) and H5N1 (85 %). Gastrointestinal symptoms are more common with H5N1 (98 %) compared to H7N9 (13 %) infections [26–28]. H7 infections had previously been associated with conjunctivitis. Two small outbreaks occurred previously, in the Netherlands (2003) and Canada (2004), both originated in poultry and resulted in a single fatal case as a result of pneumonia in each outbreak [29].

#### Laboratory and Radiological Features

Key laboratory features in both H5N1 and H7N9 were lymphopenia, thrombocytopenia, and raised alanine transaminase, with all three features reported more frequently in H7N9 [27–29]. Both H5N1 and H7N9 had radiological changes consistent with pneumonia, including air bronchograms, diffuse ground glass shadowing, and pleural effusions [30]. Severe disease was associated with more extensive lung pathology [31].

#### Complications and Causes of Death

The most common complication was ARDS with 76 % of H7N9 patients admitted to an intensive care unit at a median of 7 days after illness onset. Patients requiring mechanical ventilation experienced complications including ventilator-associated pneumonia, pulmonary hemorrhage, and pneumothorax. Organ dysfunctions included acute kidney injury, cardiac dilatation, arrhythmias, myocarditis, pericarditis, gastrointestinal hemorrhage, encephalitis, rhabdomyolysis, and

sepsis of unknown source. Most deaths have resulted from rapidly progressive pneumonia, typically primary influenza infection rather than secondary bacterial infection. Mortality with H7N9 is 30–35 %, with death occurring 6–48 days after onset. By contrast, H5N1 mortality is 60–70 %, with patients dying sooner at 4 to 29 days. Mortality rates are based on the outcomes of hospitalized patients and may overestimate the true mortality rate [26–28]. Yu's modeling study, using assumptions about sentinel surveillance coverage and health-seeking behavior, suggests that H7N9 mortality could be as low as 16 %, which is nevertheless 100-fold higher than that of seasonal influenza [32].

#### Risk Factors for Severe Disease and Death

Risk factors of mortality are different between H5N1 and H7N9, particularly for age. H7N9 patients older than 60 had higher mortality (49 %) compared to those under 16 (18 %), whereas the opposite is true for H5N1, which saw 89 % of patients under 15 succumbing. In a multivariate analysis, coexisting medical conditions was the only other predictor for death from H7N9, despite this being a confounder with older age [26–28].

Severity of disease is believed to be driven by the release of pro-inflammatory cytokines. Although studied in a few cases, levels of IL-2, IL-6, and  $\gamma$ -IFN measured post-mortem were found to be higher in patients infected with H5N1 compared to uninfected individuals [33, 34]. Testing of acute sera from H7N9 patients also indicated that levels of particular cytokines were predictive of more severe outcomes, which may suggest possible therapeutic approaches [35].

## Diagnosis

Diagnosis should be considered for individuals presenting with travel exposure in H5N1- or H7N9-affected areas, with or without poultry exposure. For residents in avian influenza-affected areas, influenza-like illness with fever and cough should prompt consideration of possible avian influenza, especially if disease is severe and rapidly progressive, or if patient has history of exposure to poultry within the previous 2 weeks, or contact with an infected person.

For both H5N1 and H7N9, definitive diagnosis can be confirmed by PCR or viral culture of respiratory samples including nasal/throat swabs, sputum, or bronchoalveolar lavage samples. Paired sera that meet the WHO criteria may also be useful for detecting asymptomatic cases, for retrospective diagnosis, and for epidemiological studies [10].

## Treatment

### Antivirals

Specific antivirals for these influenza strains are primarily the neuraminidase inhibitors oseltamivir and zanamivir, with newer agents such as peramivir available for compassionate or emergency use in different countries. Agents that block the influenza matrix protein 2 ion channel such as amantadine are not recommended due to resistance.

Neuraminidase inhibitors stop the virus from exiting the host cell, thereby acting to reduce viral loads in the blood. H5N1 survivors have demonstrated lower levels of the virus in their blood than non-survivors [36]. In a subgroup of 38 patients treated with oseltamivir, it took an average of 11 days for viremia to drop to undetectable levels [27, 28]. Timing of oseltamivir initiation (less than or more than 5 days) was not a significant risk factor for death [26].

In seasonal influenza, starting treatment within 72 h of the onset can reduce the duration of symptoms [36]. Observational studies of hospitalized patients show that the use of oseltamivir can reduce mortality, and there is clinical benefit even when started after 72 h [37••]. Although the effectiveness of oseltamivir in treating H7N9 is not proven, there are data to support its effectiveness against H5N1. A retrospective, observational study of 308 cases from 12 countries looking at oseltamivir efficacy across several H5N1 clades demonstrated 49 % reduction in mortality in those who received oseltamivir compared to those who did not [38].

Oseltamivir is currently recommended for treatment of confirmed and probable cases of avian influenza. Pre-emptive treatment may be considered in close contacts and in suspect cases requiring hospitalization [39]. Although early treatment likely confers greater benefit, confirmed and probable cases should receive neuraminidase inhibitor treatment

even if they present more than 48 h after illness onset. Longer courses of treatment are recommended for those with severe illness. Animal data suggests that H5N1 clades circulating more recently have required higher doses of neuraminidase inhibitor for the same antiviral effects. Using higher doses of oseltamivir for longer durations may therefore be considered in those with severe infection or immunocompromise, although the clinical benefit remains unproven [40].

Unfortunately, oseltamivir resistance has been reported with H5N1 as early as 2005 [41]. A single mutation at position 274 (H274Y) confers resistance to neuraminidase inhibitors, resulting in reduced efficacy and poor clinical outcomes. To date, most strains of H7N9 remain susceptible to neuraminidase inhibitors.

### Immunologic Therapies

Plasma from convalescent patients has been used in several emerging infection outbreaks, including Ebola, SARS, and most recently H1N1 [42–44]. Phase 1 studies have been conducted using polyclonal equine immunoglobulin against H5N1 by Fab'entech, a French biopharmaceutical company specializing in developing immunotherapies. Purification for the immunoglobulin F(ab') fragments permits reduced reactogenicity [45]. Used early, this passive protection may prevent descent into the cytokine cascade, which is thought to cause severe disease. Close to 60 % of patients in the H7N9 case series were given intravenous immunoglobulin, but there is no analysis as to effectiveness [26].

Adjunctive therapy for H5N1 and H7N9 remains in the experimental stage. High doses of corticosteroids are generally not recommended and remain controversial. In a randomized trial of Vietnamese patients with H5N1, all four patients given dexamethasone died. Two patients treated with steroids in the 1997 Hong Kong outbreak survived [46]. In the first H7N9 outbreak, 62 % of patients received corticosteroids [26]. In summary, there is sparse evidence that adjunctive therapies significantly improve outcomes for avian influenza. The mainstay of treatment is supportive care including mechanical ventilation, and access to intensive care may be an important factor for survival.

## Prevention

### Infection Prevention and Control

Sporadic human cases of H5N1 continue to occur, primarily in Southeast Asia. Imported H7N9 cases have been reported in several Asian countries in travelers from Chinese provinces with ongoing transmission. The first such case turned up in Taiwan; a traveler returned from Jiangsu, China, on April 9

2013, and developed fever 3 days later [47]. Travel-associated H7N9 importations have also been reported in Malaysia and Hong Kong [48, 49]. Currently, the risk level does not warrant travel restrictions to particular countries [50]. The US Centers for Disease Control and Prevention (CDC) advises individuals traveling in avian influenza-affected regions to avoid touching dead or live birds, eat only food that is fully cooked, practice good hygiene, and seek medical advice early if ill [51, 52].

Some countries have adopted thermal screening at airports. Those with fever who have been in areas with ongoing transmission may be investigated and quarantined until confirmatory tests are completed. These suspected or confirmed cases of avian influenza should be admitted to facilities that permit airborne isolation precautions, if available. Although influenza is generally transmitted via droplet spread, some airborne transmission is possible with medical procedures. Given the high morbidity and mortality with H5N1 and H7N9 and lack of highly effective therapy, an abundance of caution would lead to recommending the use of N95 respirators, gowns, goggles, and eye protection in order to minimize risk to health care workers and other hospitalized patients.

### Poultry Controls

Control remains a challenge because avian influenza can spread through poultry and wild bird populations, causing both symptomatic and asymptomatic infection. WHO has released guidance for countries undertaking poultry control activities [53]. The 1997 Hong Kong H5N1 outbreak was brought to an end by culling over a million poultry, however came a cost of many lost livelihoods and over US\$10 billion [54]. According to Food and Agriculture Organisation (FAO) estimates, 20 % of Indonesian workers on industrial farms lost their jobs as a result of poultry culling in 2004 [53].

However, the demand for meat and poultry in China continues to rise; from 1985 to 2011, annual per capita poultry consumption increased threefold from 3.2 to 10.6 kg [55]. After the 1997 outbreak, new regulations imposed on wet markets included regular cleaning of transport cages, banning overnight poultry storage, and screening Chinese farms exporting poultry to Hong Kong. These measures reduced avian carriage of H9N2 from 10 to 1 % [55]. Live bird market closures in Shanghai, Hangzhou, Huzhou, and Nanjing areas appear to have reduced H7N9 infections by 99 %. The rapid drop in cases after closing markets indicates that the mean H7N9 incubation period is 3.3 days [14]. WHO also advises that poultry should be slaughtered away from other food products to avoid contamination, different species should be kept apart, and there should be surveillance for sick poultry [53]. In countries where most poultry are “backyard” chickens rather than farms, poultry vaccination may be more useful, as was the experience in Vietnam in 2004 [53].

### Vaccines

Pre-pandemic vaccination can potentially prevent millions of people from succumbing to novel influenza virus. Challenges for pandemic vaccine manufacturers include short timelines and large amounts of vaccine to protect entire populations. Ideally, the product should facilitate mass vaccination and provide cross clade protection in anticipation of subsequent waves of the pandemic. Influenza vaccine production is dependent on embryonated chicken eggs for culture, which is the rate-limiting production factor currently. Egg-independent vaccine production strategies are undergoing active investigation. Examples include cell-derived whole-virus inactivated vaccines which can take 1–3 months to manufacture, compared to 5–6 months for egg-based vaccines which have been tested in phase 3 trials. Other vaccine types that are still in trial stage include recombinant protein-based vaccines, virus-like particle-based vaccines, DNA vaccines, and viral vector-based vaccines [reviewed in 56].

Novel influenza strains are less immunogenic than viruses that are genetically closer to strains that we may have encountered previously either through vaccine or disease. Much of

**Table 2** Advice for travelers to areas affected by avian influenza

General advice
No travel restrictions in place (but check WHO alert and response information before travel)
No vaccination against avian influenza available for travelers
Activities to avoid
Do not touch birds, pigs, or other animals.
Avoid live birds or poultry markets.
Avoid other markets or farms with animals (wet markets).
Food advice
Eat food that is fully cooked.
Do not eat or drink dishes that include blood from any animal.
Do not eat food from street vendors.
Hygiene measures
Wash your hands often.
If soap and water are not available, clean your hands with hand sanitizer containing at least 60 % alcohol.
Do not touch your eyes, nose, or mouth. If you need to touch your face, make sure your hands are clean.
Cover your mouth and nose with a tissue or your sleeve (not your hands) when coughing or sneezing.
Try to avoid close contact, such as kissing, hugging, or sharing eating utensils or cups, with people who are sick.
If you become unwell
Seek medical advice if you become unwell with fever, cough, or shortness of breath.
Delay travel home until better.
See a doctor if you become sick during or up to 2 weeks after travel to an area where avian influenza cases have been reported recently.

the focus on pandemic vaccine production has been on dose-sparing formulations used alongside adjuvants. The most immunogenic of these preparations has been the squalene adjuvants (MF59, ASO3). An MF59-adjuvanted inactivated subunit H5N1 vaccine demonstrated seroprotection at doses as low as 7.5 µg over a two-dose schedule. This vaccine derived from a clade 1 virus also demonstrated cross protection against the clade 2 virus [57]. Similar results were obtained with ASO3-adjuvanted H1N1 vaccine in children; however, post marketing surveillance of the pandemic H1N1-adjuvanted vaccine detected an increase in narcolepsy in children aged up to 18 with symptoms most likely to start in the first 6 months post vaccination [58, 59]. Furthermore, alum is the only adjuvant that is approved for use in the US market; however, alum-adjuvanted vaccines have had variable results. Currently, there are three licensed H5N1 vaccines in various regions of the world, and all three are split virion, inactivated vaccines: Sanofi Pasteur's split virion alum-adjuvanted vaccine (US), GlaxoSmithKline's Prepandrix containing ASO3 (European Union), and CSL Limited's Panvax (Australia). No vaccines are licensed as of yet of H7N9, but several candidate strains are registered with WHO as part of preparedness planning. None of these vaccines are routinely advised for travelers and stocks are currently held by various governments for pandemic use.

#### Traveler-Specific Issues

A US survey of 1301 travelers due to visit Asia found that although the majority of travelers were aware of general influenza prevention, there was less awareness of H5N1 transmission risks, and this was more marked among Asians, foreign-born travelers, and those not working in animal or health care [60]. To underscore this issue, the first case of H5N1 was imported into Canada by a returning traveler. The patient was ethnically Chinese, resided in Canada, and had spent a month in Beijing. She developed symptoms on her way home and died soon after [6]. A survey of Chinese communities living in Europe demonstrated that the perceived risks and severity of avian influenza were lower compared to the general population [59]. Travelers visiting friends and family (VFR) in avian influenza-affected countries may therefore be at increased risk compared to other travelers to the region (Table 2).

#### Conclusion

For the coming year, H5N1 caseloads are expected to continue at present levels, but we anticipate that H7N9 cases may increase as we enter the Northern Hemispheric winter of 2014–2015, especially as intensive surveillance in China

continues. Individuals may continue to be at risk due to poultry exposures. The risk of a global pandemic remains low currently, in the absence of sustained, efficient transmission between humans. However, with reservoirs that cannot be completely eradicated, these pre-pandemic threats will remain with us for the foreseeable future. Appropriate preventive measures will protect most travelers to areas affected by avian influenza, but those at higher risk may include VFR travelers and immigrants who are less likely to be reached by pre-travel advice. All three avian influenza strains still carry high morbidity and mortality, with proven treatment options limited to antivirals and supportive care.

#### Compliance with Ethics Guidelines

**Conflict of Interest** Poh Lian Lim has no disclosures relevant to this work.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by the authors.

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