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SUPPLEMENT ARTICLE

The Global Threat of Animal Influenza Viruses of Zoonotic Concern: Then and Now

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Animal influenza viruses can reassort or mutate to infect and spread sustainably among people and cause a devastating worldwide pandemic. Since the first evidence of human infection with an animal influenza virus, in 1958, 16 different novel, zoonotic influenza A virus subtype groups in 29 countries, Taiwan, and Hong Kong have caused human infections, with differing severity and frequency. The frequency of novel influenza virus detection is increasing, and human infections with influenza A(H5N1) and A(H7N9) viruses are now annual seasonal occurrences in Asia. The study of the epidemiology and virology of animal influenza viruses is key to understanding pandemic risk and informing preparedness. This supplement brings together select recent articles that look at the risk of emergence and transmission of and approaches to prevent novel influenza virus infections.

Keywords. Influenza; novel; zoonotic; global; pandemic.

Influenza presents 2 major challenges to public health. The first comes from a small group of seasonal human influenza viruses that cause respiratory disease worldwide, especially notable as annual epidemics in temperate climes. Although seasonal influenza is generally of low severity, high annual attack rates globally result in substantial global respiratory and circulatory mortality, especially in high-risk groups such as the elderly. Seasonal influenza is vaccine preventable, although because the virus is constantly evolving, vaccine requires annual or semiannual updates to maintain its effectiveness. The second challenge is the threat posed by the emergence of a novel virus from a great reservoir of diverse influenza A viruses that exist among birds and other animals. These viruses can leap unpredictably across the species barrier to cause human illness and global pandemics with high case-fatality rates, such as occurred in 1918 and for which widespread vaccination may not be possible in time to prevent a significant number of illnesses and deaths. Key to this capability of influenza A viruses to change unpredictably is a segmented RNA genome that allows reassortment to create new viruses that are novel to the human immune system and can cause severe disease. The constant adaptation and exchange of genes between influenza viruses in different species, including at the animal-human interface, continue to pose a critical challenge to the prediction of and preparation for the emergence of pandemic viruses.

In this supplement, we bring together a selection of articles that reflect work to better understand influenza A viruses of zoonotic concern, their risk to public health and global health security, and effective measures to prevent their emergence as pandemic agents.

HISTORY AND EPIDEMIOLOGY OF ANIMAL INFLUENZA VIRUSES OF ZOONOTIC CONCERN

Although similarities in pathology and clinical features between swine and human pandemic influenza were first noted in 1918 by a veterinarian [1, 2], serologic evidence of human infection with a swine influenza virus was not reported for another 40 years, in 1958 [3]. Conclusive evidence that influenza viruses could be transmitted from swine to humans would come even later, in 1976 [4]. For >60 years now, public health bodies such as the World Organization for Animal Health, the Food and Agriculture Organization, and the World Health Organization (WHO) have coordinated efforts to monitor and characterize human and animal influenza viruses. In 1952, the WHO initiated a network, now called the Global Influenza Surveillance and Response System (GISRS), to support detection and characterization of influenza viruses globally, gathering these data to monitor activity and determine vaccine composition. The GISRS network, celebrating its 65th anniversary this year, includes 143 national influenza centers around the globe that conduct polymerase chain reaction testing of specimens to characterize influenza virus type and subtype and to isolate viruses in culture. These centers then submit viruses and associated specimens to one of 6 reference laboratories for further antigenic and genetic characterization, such as whole-genome sequencing [5]. This system provides critical support for the global detection and full characterization of human infections with novel influenza viruses.

Since 2000, there has been a notable increase in the number of novel influenza virus infections reported globally, including the expansion of high-pathogenicity avian influenza (HPAI) A(H5N1)

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virus throughout much of the world, the influenza A(H1N1) virus pandemic arising in the Americas, and the emergence of low-pathogenicity avian influenza (LPAI) and HPAI A(H7N9) viruses in China (of note, low or high pathogenicity in avian viruses refers to virus pathogenicity in poultry and not humans).

We collated reports from the literature, WHO reports, CDC surveillance data, and other sources to create an inventory of novel influenza virus subtype groups that have caused human infections, from the first serologically evidenced case in 1958 through May 2017. We grouped novel viruses on the basis of hemagglutinin and neuraminidase subtype and, for avian influenza viruses, by low and high pathogenicity. We included infections evidenced by both serologic and virologic methods but excluded deliberate infections of volunteers. We did not include the 1968 pandemic influenza A(H3N2) virus (which contained avian influenza virus genes) and the 2009 pandemic influenza A(H1N1) virus (which contained swine influenza virus genes). To date, 16 novel animal-derived influenza virus subtype groups have been detected and characterized as a cause of human infections either acquired in or imported to 29 countries, Taiwan, and the Hong Kong Special Administrative Region (SAR) among 6 continents (Table 1). In several countries, multiple separate clusters of infections have occurred over time. Avian and porcine reservoirs are usually implicated virologically or epidemiologically in the transmission to humans, but occasionally other animals, such as seals and cats, have also been associated with influenza in humans. In some instances, transmission has been associated with relatively intense exposure, such as a laboratorian who became infected after an influenza A(H7N7) virus–infected seal sneezed in his face [6], persons depopulating infected poultry flocks [7], or, recently, a veterinarian caring for an infected cat [8]. Often, exposure to infected live or sick birds is reported, typically backyard chickens or in live-bird markets, but occasionally no or little exposure to an infected animal is reported. A subset of influenza A viruses (H5N1, H7N9, and H5N6) are characterized by severe lower respiratory tract infections and high reported case-fatality proportions in humans. However, for many novel influenza viruses, small numbers of human cases make it difficult to draw firm conclusions, especially because milder zoonotic influenza virus infections are less likely to be detected than severe infections. Milder illnesses are characterized by influenza-like symptoms, such as fever and cough, and occasionally by conjunctivitis, especially for some lineages of H7 viruses.

The increase in reports in recent years of human infections with novel viruses is, in large part, due to efforts by the WHO, the Centers for Disease Control and Prevention (CDC), and other international partners to increase surveillance capacity, including greater use of influenza virus diagnostics, worldwide after the global emergence of influenza A(H5N1) virus. As a result, since 2000, the number of countries reporting data to

Table 1. Summary of Virologically or Serologically Confirmed Reports of Zoonotic Influenza A Virus Infections in Humans, by Subtype Group

Subtype Group	Year First Detected	Year Last Detected	Countries[a] of Occurrence	Confirmed Cases, No.; Confirmed Fatalities, No.	Representative Reference(s) for Each Country
H1N1v	1958	2016	Canada, China, Czechoslovakia, Italy, Netherlands, Russia, Spain, Switzerland, Thailand, US	41; 6	[3, 9–16]
HPAI H7N7	1959	2003	Australia, US, Netherlands	91; 1	[7, 17, 18]
LPAI H7N7	1979	2013	US, Italy, United Kingdom	5; 0	[6, 19, 20]
H3N2v	1992	2017	Canada, Hong Kong SAR, Netherlands, US, Vietnam	380; 2	[14, 21–24]
HPAI H5N1	1997	2017	Azerbaijan, Bangladesh, Cambodia, Canada,[b] China, Djibouti, Egypt, Hong Kong, Indonesia, Iraq, Laos, Myanmar, Nigeria, Pakistan, Thailand, Turkey, Vietnam	856; 453	[25–27]
LPAI H9N2	1998	2015	Bangladesh, China, Egypt, Hong Kong, SAR[b]	36; 1	[28–31]
LPAI H7N2	2003	2017	United Kingdom, US	7; 0	[8, 32, 33]
HPAI H7N3	2004	2012	Canada, Mexico	4; 0	[34, 35]
LPAI H10N7	2004	2012	Australia, Egypt	4; 0	[36, 37]
LPAI H7N3	2006	2006	United Kingdom	1; 1	[18]
H1N2v	2007	2015	Brazil, Philippines, US	10; 0	[14, 16, 38]
LPAI H7N9	2013	2017	Canada,[b] China, Malaysia,[b] Taiwan[b]	1393; 534	[39]
LPAI H10N8	2013	2014	China	3; 2	[40]
LPAI H6N1	2013	2013	Taiwan	1; 0	[41]
HPAI H5N6	2014	2016	China	17; 12	[42]
HPAI H7N9	2017	2017	China, Taiwan[b]	8; 4	[43]

Adapted and updated from articles by Perdue and Swayne [25], Myers et al [44], and Freidl et al [45]. Influenza viruses that normally circulate in swine are called "variant" viruses and are designated by the letter *v* (eg, "H1N1v") when they occur in humans. Human infections with novel influenza viruses, including variant influenza viruses, were notifiable diseases only after the revision of the International Health Regulations in 2005.

Abbreviations: LPAI, low-pathogenicity avian influenza virus; HPAI, high-pathogenicity avian influenza virus; SAR, Special Administrative Region of China.

[a]Includes Taiwan and Hong Kong SAR.

[b]Imported case(s).

the GISRS has increased >4-fold to approximately 130 countries (Figure 1A). The level of reporting, as measured by the number of positive results of seasonal influenza virus tests sent to the WHO, shows an even more pronounced rise, increasing sharply in 2009 during the pandemic and persisting to date (Figure 1B). It is likely that more-widespread testing for influenza virus since 2013 in cases of severe pneumonia during the annual waves of influenza A(H7N9) virus infection in China was a factor in detecting recent infections due to influenza A(H6N1), A(H5N6), A(H10N8) viruses and HPAI A(H7N9) virus for the first time.

FACTORS LEADING TO EMERGENCE

The host and viral factors that can predict zoonotic novel influenza virus infections in humans and, most importantly, the further ability of such factors to transmit from human to human are complex, interrelated, and not fully understood. Some virus genes coding for receptor affinity, temperature tolerance, viral replication, and mammalian adaptation certainly play a role [46], and these are constantly adapting and reassorting in the extensive wild and domestic bird reservoir. In addition, human host factors play a part; preexisting immunity to previous influenza virus infection of different but related subtypes, comorbidities, and host genetics, such as HLA alleles, will play a role in the likelihood of zoonotic infection and disease. Finally, increased density and transportation of animals has likely allowed for greater opportunity for reassortment and adaptation of influenza viruses [5].

The frequency, clinical picture, and epidemiologic characteristics of novel influenza virus infections in humans are therefore unpredictable, challenging the assessment of the potential public health risk and the planning for pandemic preparedness. For example, the influenza A(H7N9) virus that emerged in China in 2013 has led to death in 40% of reported infections in people, but prior H7 infections were associated with mild upper respiratory tract illness and conjunctivitis [47]. The emergence of the 2009 pandemic of a swine-origin influenza A(H1N1) virus in the Americas was entirely unexpected because the concern had been focused on influenza A(H5N1) viruses that had emerged in Asia.

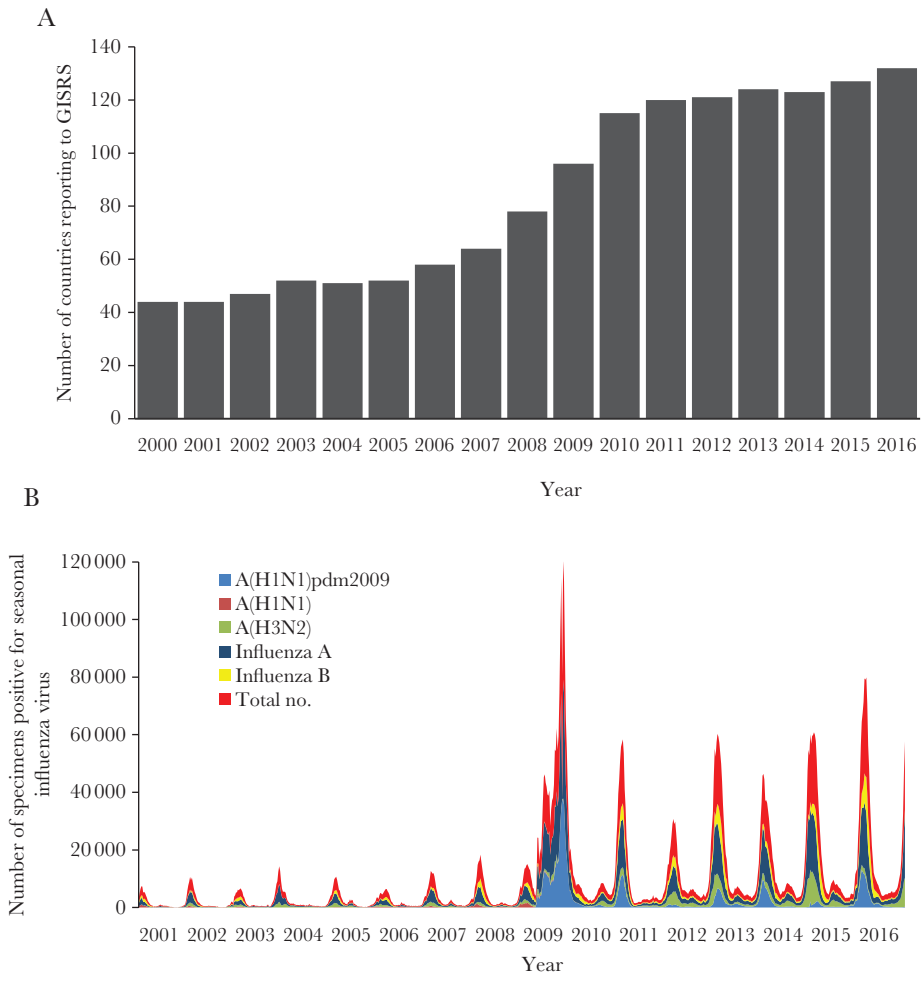

Figure 1. *A*, Number of countries reporting to the Global Influenza Surveillance and Response System, by year, since 2000. *B*, Total number of seasonal influenza virus–positive specimens reported to the GISRS, by year and by influenza virus type and subtype, since 2000. Abbreviation: A(H1N1)pdm09, 2009 pandemic influenza A(H1N1) virus.

Once novel influenza viruses emerge as causes of human infections, their epidemiology can remain unpredictable. For instance, influenza A(H7N9) virus infections in China occur far more frequently than influenza A(H5N1) virus infections in the elderly, although exposure to poultry is common to both virus infections. Furthermore, as an LPAI with ability to infect poultry asymptomatically and therefore spread undetected in commercial poultry, influenza A(H7N9) virus infections have only occurred in China, unlike those due to influenza A(H5N1) virus, which spread rapidly through Southeast Asia after reemergence, despite obvious pathogenicity in the infected poultry to help target control measures.

To provide a more objective and systematic approach to characterizing the pandemic potential of the increasing number of detected novel influenza viruses, the CDC and other public health partners have developed the Influenza Risk Assessment Tool [48]. This tool evaluates 10 specific criteria and calculates a score for each virus' risk of acquiring the ability to transmit readily from person to person and, should that occur, the potential impact on public health. This risk assessment information is one input that may be used to guide vaccine development and stockpiling, research, and prepandemic preparedness [49]. Of the viruses evaluated to date, the Asian-lineage influenza A(H7N9) viruses in China have the highest risk scores [48].

Several of the articles in this supplement focus on the potential risk posed by these viruses, including risk factors and source species for transmission, human-to-human spread, and virologic characteristics, often using animal models in controlled conditions. In 2005, a new influenza A(H3N2) virus subtype spread to dogs in multiple states in the United States. A study by Pulit-Penaloza et al [50] analyzed the molecular, antigenic, and pathological features of the virus, using ferrets and mice, and found that the virus was not well adapted to humans. A similar study by Belser et al [51], analyzing HPAI A(H7N7) virus circulating in Italy that caused 3 human cases of conjunctivitis, found some moderate virulence and transmission capacity in the ferret model, suggesting some adaptation to mammalian tissues. In South Africa, Venter et al [52] found evidence of a substantial increase in seropositivity to LPAI A(H7N1) virus among exposed slaughterhouse staff after an outbreak of this virus in ostriches. LPAI A(H7N1) virus has not been reported as a pathogen of clinical human infection, but this evidence points to subclinical infection of LPAI A(H7N1) virus in humans and to ostriches as a source. In Bangladesh, a study by Chakraborty et al [53] reports 2 children with mild disease due to HPAI A(H5N1) virus in a small population-based study area. Children have tended to have less severe outcomes of infection due to both HPAI A(H5N1) and LPAI A(H7N9) viruses; however, this study strongly suggests that mild H5N1 (and therefore possibly other zoonotic influenza virus) infections of children are occurring undetected in Bangladesh. Another article on HPAI A(H5N1) virus, by Creanga et al [54], analyzes the phylogenetic relationship in Vietnam between circulating influenza A(H5N1) viruses in poultry and those in humans and concludes that poultry HPAI A(H5N1) viruses can rapidly acquire molecular markers for mammalian adaption and antiviral resistance. Liu et al [55] examine the titers of hemagglutinin antibodies in humans and ferrets to assess the cross-reactivity between antibodies against various swine influenza A(H3N2) virus variants and seasonal influenza A(H3N2) viruses. Of particular relevance is that 1 amino acid difference in the hemagglutinin of a swine influenza A(H3N2) virus variant that emerged in 2013 was sufficient to reduce the cross-reactivity of preexisting anti–influenza A(H3N2) variant virus antibodies. Last, Liu et al [56] address the critical issue of assessment of human-to-human transmission. Person-to-person transmission has been documented for several novel influenza viruses but never for >3 generations. Initially following emergence of novel influenza viruses, the extent to which human-to-human transmission is occurring may be unclear since many contacts may have had an exposure, such as to live birds, similar to that of the index case. Liu et al present an approach that they applied to human cases of avian influenza A(H7N9) virus infection in China to assess the likelihood of human-to-human spread.

MEASURES TO PREVENT NOVEL INFLUENZA VIRUS INFECTIONS

Measures to prevent zoonotic influenza virus infections include nonpharmaceutical and pharmaceutical strategies. Nonpharmaceutical measures include limiting the number of informal live-bird markets, newer designs with barriers to reduce customer exposure, and market furlough days with strategies to disinfect facilities and manage bird movement. Pharmaceutical interventions such as antiviral medication and vaccines also play a role in prevention. Poultry vaccination against avian influenza may be a useful tool in some countries. Neuraminidase inhibitors are important antivirals to treat infected humans and perhaps to prevent infection. Oseltamivir resistance has been reported in some novel influenza virus strains, and the effectiveness of these drugs is diminished if administered ≥48 hours after onset. Last, efforts to develop human novel influenza vaccines has led to licensure of 2 H5N1 vaccines in the United States and 1 in Australia and also to availability of other prepandemic vaccines for investigational or emergency use in the United States. However, use of these vaccines and development of those for other subtypes is challenged by poor immunogenicity and limited cross-protection to heterologous strains, complicating decisions to invest in vaccine stockpiles.

Two articles in this supplement assess H5N1 vaccines and their usefulness in the face of current novel influenza activity. In 2015, HPAI H5 viruses spread rapidly among domestic and wild birds in the US causing a substantial financial loss. Levine et al [57] aim to understand whether a stockpiled H5N1 vaccine may be effective against this potential zoonotic threat and report that a heterologous prime-boost strategy may broaden

the immune response and elicit some cross-protective hemagglutinin antibody responses against these H5 viruses, compared with a homologous vaccine strategy. The second study, by Jones et al [58], assesses whether H5N1 vaccines are effective in mice with protein energy malnutrition. The effect of malnutrition on vaccine performance is relevant, as a global pandemic will likely affect poorer populations disproportionately, as seen in 2009 [59]. The results suggest that H5N1 vaccines are less effective at preventing influenza A(H5N1) virus infection in mice with protein energy malnutrition than in adequately fed mice but that adjuvanted vaccines may overcome this difference and therefore may be a better choice for certain vulnerable populations. Last, 2 articles assess the usefulness of antivirals for animal viruses of zoonotic concern. Gubareva et al [60] present an approach using recombinant neuraminidase proteins to assess which molecular changes confer resistance to neuraminidase inhibitors. Havers et al [61] look at the history of antiviral policy in the United States for novel animal influenza virus infection and outline current guidance. Certain aspects are stressed in guidelines for antiviral use in novel influenza virus infection. For instance, because stopping transmission and preventing acquisition of resistance is especially important, the prophylactic dose is now recommended in the United States to be twice that recommended for seasonal influenza. This helps ensure that that subtherapeutic dose is not administered to a contact in the early stages of infection, as this would accelerate development of resistance, as was seen in some cases of influenza A(H7N9) virus infections [62].

Surveillance and research efforts have led to better monitoring and understanding of animal influenza viruses of zoonotic concern, but further understanding of the risk that different viruses pose to people, their epidemiology, and the means of preventing infection by them is critical. Continued support for influenza surveillance, laboratory capacity, and research, along with other investments in global health security, will facilitate prevention of and rapid detection and response to human infections with novel influenza viruses and to a range of other global threats.

Notes

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