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

Marc-Alain Widdowson,1,3 Joseph S. Bresee,2 and Daniel B. Jernigan2

1Division of Global Health Protection, Center for Global Health, Centers for Disease Control and Prevention (CDC), Nairobi, Kenya; and 2Influenza Division, National Center for Immunization and Respiratory Diseases, and 3Division of Global Health Protection, Center for Global Health, CDC, Atlanta, Georgia

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 an annual epidemic 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)

Correspondence: M-A. Widdowson, VetMB, MA, MSc, Division of Global Health Protection, CDC-Kenya, Center for Global Health, Centers for Disease Control and Prevention, Mbagathi Rd, PO Box 606, Village Market 00621, Nairobi, Kenya (mawiddowson@cdc.gov).

The Journal of Infectious Diseases® 2017;216(S4):S493–8

Published by Oxford University Press for the Infectious Diseases Society of America 2017. This work is written by (a) US Government employee(s) and is in the public domain in the US. DOI: 10.1093/infdis/jix331

Pandemic Threat of Zoonotic Influenza Viruses • JID 2017;216 (Suppl 4) • S493
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 by 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* of Occurrence | Confirmed Cases, No.; Confirmed Fatalities, No. | 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] |
| H5N2v         | 1992                | 2017               | Canada, Hong Kong SAR, Netherlands, US, Vietnam | 380; 2 | [14, 21–24] |
| HPAI H8N1     | 1997                | 2017               | Azerbaijan, Bangladesh, Cambodia, Canada, 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 | 36; 1 | [29–31] |
| LPAI H7N2     | 2003                | 2017               | United Kingdom, US | 7; 0 | [6, 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, China, Malaysia, Taiwan | 1393; 534 | [39] |
| LPAI H10N8    | 2013                | 2014               | China | 3; 2 | [40] |
| LPAI H8N1     | 2013                | 2013               | Taiwan | 1; 0 | [41] |
| HPAI H5N6     | 2014                | 2016               | China | 17; 12 | [42] |
| HPAI H7N9     | 2017                | 2017               | China, Taiwan | 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.

*Includes Taiwan and Hong Kong SAR.

**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
Acknowledgments. We thank Dr Gina Samaan and colleagues at the WHO Global Influenza Program, for suggestions and cover graphics; and Dr Bernard Easterday, for historical perspective.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Supplement sponsorship. This work is part of a supplement sponsored by the Centers for Disease Control and Prevention.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References
1. Kowal K, Macku M, Mensik J. Demonstration of antibodies against swine influenza virus in man. Cesk Pediatr 1961; 16:408-14.
2. Pavlish R, Easterday BC, Nelson DB, Skinner HG, Levy ME. Influenza - Wisconsin and Washington, D.C. MMWR Morb Mortal Wkly Rep 1976; 25:593.
3. Jernigan DB, Cox NJ. Human influenza: one health, one world. In: Webster RG, Monto AS, Braciale TJ, Lamb RA, ed. Textbook of influenza. 2nd ed. Hoboken, NJ: John Wiley and Sons, 2013:3–19.
4. Webster RG, Geraci J, Petersson G, Skurniss K. Conjunctivitis in human beings caused by influenza A virus of seals. N Engl J Med 1981; 304:911.
5. Koopmans M, Wilbrink B, Coyn M, et al. Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in commercial poultry farms in the Netherlands. Lancet 2004; 363:587–93.
6. World Health Organization. Monthly risk assessment summary. Influenza. http://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_01_16_2017_FINAL.pdf?ua=1. Accessed 30 May 2017.
7. de Jong JC, Paccard ME, de Ronde-Verloop FM, et al. Isolation of swine-like influenza A(H11N1) viruses from man in Switzerland and The Netherlands. Ann Ins Pasteur Virol 1988; 139:39–37.
8. Yang H, Qiao C, Tang X, Chen Y, Xin X, Chen H. Human infection from avian-like influenza A (H1N1) viruses in pigs, China. Emerg Infect Dis 2012; 18:1144–6.
9. Adiego Sancho B, Omenaca Teles M, Martinez Cuencas S, et al. Human case of swine influenza A (H1N1), Aragon, Spain, November 2008. Euro Surveill 2009; 14.
10. Winter AL, Eshaghhi A, Farrell DJ, et al. Variant influenza A (H1N1) virus infection in Canada. J Clin Virol 2013; 57:279–81.
11. Chuvakovka ZK, Rovnouzi IJ, Iasaev EI, Kim EV, Igneva TV. 3 cases of isolating the influenza A virus with human hemagglutinin H5w1 in 1983 in Alma-Ata. Vopr Virusol 1985; 30:350–6.
12. Shinde V, Bridges CB, Uyeki TM, et al. Triple-reassortant swine influenza A (H1) in humans in the United States, 2005-2009. N Engl J Med 2009; 360:2616–25.
13. Rovida F, Piralla A, Marzani FC, et al. Swine influenza A (H1N1) virus (SIV) infection requiring extracorporeal life support in an immunocompetent adult patient with indirect exposure to pigs, Italy. October 2016. Euro Surveill 2017; 22:30456.
14. Komadina N, Roque V, Thawatsupha P, et al. Genetic analysis of two influenza A (H1) swine viruses isolated from humans in Thailand and the Philippines. Viruses Genes 2007; 35:161–5.
15. De Lay PD, Casey HL, Tubash HS. Comparative study of fowl plague virus and a virus isolated from man. Public Health Rep 1967; 82:615–20.
16. Taylor HR, Turner AJ. A case report of fowl plague keratoconjunctivitis. Br J Ophthalmol 1977; 61:86–8.
17. Puzelli S, Rizzo C, Fabiani C, et al. Influenza A(H7N7) Virus among Poultry Workers, Italy, 2013. Emerg Infect Dis 2016; 22:1512–3.
18. Kurtz J, Manvell RJ, Banks J. Avian influenza virus isolated from a woman with conjunctivitis. Lancet 1996; 348:901–2.
19. Claas EC, Kawaoka Y, de Jong JC, Masurel N, Webster RG. Infection of children with avian-human reassortant influenza virus from pigs in Europe. Virology 1994; 204:453–7.
20. Gregory V, Lim W, Cameron K, et al. Infection of a child in Hong Kong by an influenza A H3N2 virus closely related to viruses circulating in European pigs. J Gen Virol 2001; 82:1397–406.
21. Olsen CW, Karasin AI, Carman S, et al. Triple reassortant H3N2 influenza A viruses, Canada, 2005. Emerg Infect Dis 2006; 12:1132–5.
22. Vietnam reports first human case of H3N2 swine flu. Thanh Nien News. 16 February 2012. http://www.thanhniennews.com/health/vietnam-reports-first-human-case-of-h3n2-swine-flu-8302.html. Accessed 1 May 2017.
23. Perdue ML, Swayne DE. Public health risk from avian influenza viruses. Avian Dis 2005; 49:317–27.
24. Mounts AW, Kwong H, Izurieta HS, et al. Case-control study of risk factors for avian influenza A (H5N1) disease, Hong Kong, 1997. J Infect Dis 1999; 180:505–8.
25. World Health Organization. Cumulative number of confirmed human cases of avian influenza A(H5N1) reported to WHO. http://www.who.int/influenza/human_animal_interface/2017_04_20_tableH5N1.pdf?ua=1. Accessed 31 May 2017.
26. Peiris M, Yuen KY, Leung CW, et al. Human infection with influenza H9N2. Lancet 1999; 354:916–7.
27. Guo Y, Li J, Cheng X. Discovery of men infected by avian influenza A (H9N2) virus. Zhonghua Shi Yan He Lin Chugang Bing Du Xue Za Zhi 1999; 13:105–8.
28. Shannuganathkum R, Feeo ZM, Jones-Engel L, et al. Antigenic and molecular characterization of avian influenza A(H9N2) viruses, Bangladesh. Emerg Infect Dis 2013; 19:1393–1402.
29. World Health Organization. Monthly risk assessment summary. http://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_3_March_2015.pdf?ua=1. Accessed 23 May 2017.
30. Ostrowsky B, Huang A, Terry W, et al. Low pathogenic avian influenza A (H7N2) virus infection in immunocompromised adult, New York, USA, 2003. Emerg Infect Dis 2012; 18:1128–31.
Avian influenza A(H7N2) outbreak in the United Kingdom. Euro Surveill 2007; 12:E070531.2.

Tweed SA, Skowronski DM, David ST, et al. Human illness from avian influenza H7N3, British Columbia. Emerg Infect Dis 2004; 10:2196–9.

Centers for Disease Control and Prevention. Notes from the field: Highly pathogenic avian influenza A (H7N3) virus infection in two poultry workers—Jalisco, Mexico, July 2012. MMWR Mortal Morb Wkly Rep 2012; 61:726–7.

Arzey GG, Kirkland PD, Arzey KE, et al. Influenza virus A (H10N7) in chickens and poultry abattoir workers, Australia. Emerg Infect Dis 2012; 18:814–6.

PanAmerican Health Organization. Avian influenza virus A (H10N7) circulating among humans in Egypt. 2004. http://www1.paho.org/bq/dmdocuments/2010/Aavian_Influenza_Egypt_070503.pdf. Accessed 20 April 2017.

Resende PC, Born PS, Matos AR, et al. Whole-genome characterization of a novel human influenza A(H1N2) virus variant, Brazil. Emerg Infect Dis 2017; 23:152–4.

World Health Organization. Influenza at the human-animal interface: summary and assessment, 16 March to 20 April 2017. http://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_04_20_2017.pdf?ua=1. Accessed 30 April 2017.

Chen S, Li Z, Hu M, et al. Knowledge, attitudes, and practices (KAP) relating to avian influenza (H10N8) among farmers’ markets workers in Nanchang, China. PLoS One 2015; 10:e0127120.

Wei SH, Yang JR, Wu HS, et al. Human infection with avian influenza A H6N1 virus: an epidemiological analysis. Lancet Respir Med 2013; 1:771–8.

Jiang H, Wu P, Uyeki TM, et al. Preliminary epidemiologic assessment of human infections with highly pathogenic avian influenza A(H5N6) virus, China. Clin Infect Dis 2017. In press.

Zhou L, Tan Y, Kang M, et al. Preliminary epidemiology of human infections with highly pathogenic avian influenza A(H7N9) virus, China, 2017. Emerg Infect Dis 2017; 23.

Myers KP, Olsen CW, Gray GC. Cases of swine influenza in humans: a review of the literature. Clin Infect Dis 2007; 44:1084–1094.

Freid G5, Meijer A, de Bruin E, et al. Influenza at the animal-human interface: a review of the literature for virological evidence of human infection with swine or avian influenza viruses other than A(H5N1). Euro Surveill 2014; 19.

Centers for Disease Control and Prevention. H5N1 Genetic Changes Inventory. https://www.cdc.gov/flu/avian Flu/h5n1/inventory.htm. Accessed 30 May 2017.

Belser JA, Bridges CB, Katz JM, Tumpey TM. Past, present, and possible future human infection with influenza virus A subtype H7. Emerg Infect Dis 2009; 15:859–65.

Centers for Disease Control and Prevention. Summary of Influenza Risk Assessment Tool (IRAT) results. https://www.cdc.gov/flu/pandemic-resources/monitoring/irat-virus-summaries.htm. Accessed 28 April 2017.

Cox NJ, Trott SC, Burke SA. Pandemic preparedness and the influenza risk assessment tool (IRAT). Curr Top Microbiol Immunol 2014; 385: 119–36.

Pulit-Penaloza JA, Simpson N, Yang H, et al. Assessment of molecular, antigenic, and pathological features of canine H3N2 influenza viruses that recently emerged in the U.S. J Infect Dis 2017; 216(Suppl 4):S499–507.

Belser JA, Creager HM, Zeng H, Maines TR, Tumpey TM. Pathogenesis, transmissibility, and tropism of a highly pathogenic avian influenza A (H7N7) virus associated with human conjunctivitis in Italy. 2013. J Infect Dis 2017; 216(Suppl 4):S508–11.

Venter M, Teunissen FK, Buys A, et al. Risk of human infections with highly pathogenic H5N2 and low pathogenic H7N1 Avian Influenza strains during outbreaks in ostriches in South Africa. J Infect Dis 2017; 216(Suppl 4): S512–9.

Chakraborty A, Rahman M, Khan SU, et al. Mild respiratory illness among young children caused by highly pathogenic avian influenza A (H5N1) virus infection in Dhaka, Bangladesh, 2011. J Infect Dis 2017; 216(Suppl 4):S520–8.

Creanga A, Hang NLK, Cuong VD, et al. Highly pathogenic avian influenza A(H5N1) viruses at the animal-human interface in Vietnam during 2003 to 2010. J Infect Dis 2017; 216(Suppl 4):S529–38.

Liu F, Veguilla V, Gross FL, et al. Priming with seasonal influenza A(H3N2) virus impacts the age-related prevalence of serum cross-reactive hemagglutination-inhibition antibodies to swine-origin influenza A(H3N2) variants. J Infect Dis 2017; 216(Suppl 4):S539–47.

Liu B, Havers FP, Zhou L, et al. Clusters of human infections with avian influenza A(H7N9) virus in China, March 2013—June 2015. J Infect Dis 2017; 216(Suppl 4):S548–54.

Levine M, Holiday C, Liu F, et al. Cross-reactive antibody responses to novel H5Nx influenza viruses following homologous and heterologous prime boost vaccination with a stockpiled a(h5n1) vaccine. J Infect Dis 2017; 216(Suppl 4):S555–9.

Jones EN, Amoah S, Cao W, Sambhara S, Gangappa S. An advantaged A(H5N1) subvirion vaccine elicits virus-specific antibody response and leads to enhanced protection against lethal influenza viral challenge in mouse model of protein energy malnutrition. J Infect Dis 2017; 216(Suppl 4):S566–5.

Dawood FS, Iuliano AD, Reed C, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. Lancet Infect Dis 2012; 12(9):687–95.

Gubareva LV, Sleeman K, Guo Z, et al. Drug susceptibility evaluation of an influenza A(H7N9) virus in China, March 2013—June 2015. J Infect Dis 2017; 216(Suppl 4):S560–5.

Liu B, Havers FP, Zhou L, et al. Clusters of human infections with avian influenza A(H7N9) virus at the animal-human interface in Vietnam during 2003 to 2010. J Infect Dis 2017; 216(Suppl 4):S529–38.

Chakraborty A, Rahman M, Khan SU, et al. Mild respiratory illness among young children caused by highly pathogenic avian influenza A (H5N1) virus infection in Dhaka, Bangladesh, 2011. J Infect Dis 2017; 216(Suppl 4):S520–8.

Creanga A, Hang NLK, Cuong VD, et al. Highly pathogenic avian influenza A(H5N1) viruses at the animal-human interface in Vietnam during 2003 to 2010. J Infect Dis 2017; 216(Suppl 4):S529–38.

Liu F, Veguilla V, Gross FL, et al. Priming with seasonal influenza A(H3N2) virus impacts the age-related prevalence of serum cross-reactive hemagglutination-inhibition antibodies to swine-origin influenza A(H3N2) variants. J Infect Dis 2017; 216(Suppl 4):S539–47.

Liu B, Havers FP, Zhou L, et al. Clusters of human infections with avian influenza A(H7N9) virus in China, March 2013—June 2015. J Infect Dis 2017; 216(Suppl 4):S548–54.

Levine M, Holiday C, Liu F, et al. Cross-reactive antibody responses to novel H5Nx influenza viruses following homologous and heterologous prime boost vaccination with a stockpiled a(h5n1) vaccine. J Infect Dis 2017; 216 (Suppl 4):S555–9.

Jones EN, Amoah S, Cao W, Sambhara S, Gangappa S. An advantaged A(H5N1) subvirion vaccine elicits virus-specific antibody response and leads to enhanced protection against lethal influenza viral challenge in mouse model of protein energy malnutrition. J Infect Dis 2017; 216(Suppl 4):S566–5.

Dawood FS, Iuliano AD, Reed C, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. Lancet Infect Dis 2012; 12(9):687–95.

Gubareva LV, Sleeman K, Guo Z, et al. Drug susceptibility evaluation of an influenza A(H7N9) virus by analyzing recombinant neuraminidase proteins. J Infect Dis 2017; 216(Suppl 4):S566–5.

Havers FP, Uyeki TM, Fry AM. A historical review of centers for disease control and prevention antiviral treatment and postexposure chemoprophylaxis guidance for human infections with novel influenza A viruses associated with severe human disease. J Infect Dis 2017; 216(Suppl 4):S775–80.

Marjuki H, Mishin VP, Chesnakov AP, et al. Characterization of drug-resistant influenza A(H7N9) variants isolated from an oseltamivir-treated patient in Taiwan. J Infect Dis 2015; 211:249–57.