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Review Article

Literature Review on Avian Influenza Virus Prevalence in Birds and Humans

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Abstract

Avian influenza viruses are now widely recognized as important threats to agricultural biosecurity and public health, and as the potential source for pandemic human influenza viruses. Human infections with avian influenza viruses have been reported from Asia (H5N1, H5N2, H9N2), Africa (H5N1, H10N7), Europe (H7N7, H7N3, H7N2), and North America (H7N3, H7N2, H11N9). Direct and indirect public health risks from avian influenza are not restricted to the highly pathogenic H5N1 "bird flu" virus and include low pathogenic as well as high pathogenic strains of other avian influenza virus subtypes, e.g. H1N1, H7N2, H7N3, H7N7, and H9N2. Research has shown that the 1918 Spanish Flu pandemic was caused by an H1N1 influenza virus of avian origins, and during the past decade, fatal human disease and human-to-human transmission has been confirmed among persons infected with H5N1 and H7N7 avian influenza viruses. Our ability to accurately assess and map the potential economic and public health risks associated with avian influenza outbreaks is currently constrained by uncertainties regarding key aspects of the ecology and epidemiology of avian influenza viruses in birds and humans, and the mechanisms by which highly pathogenic avian influenza viruses are transmitted between and among wild birds, domestic poultry, mammals, and humans.

Keywords: Avian Influenza; Human Influenza

Introduction

Avian influenza or bird flu is a highly contagious acute viral disease that can occur in epidemics and cross-border forms in poultry. Influenza A viruses are the etiological agent of avian influenza and belong to the *Orthomyxoviridae* family. Influenza viruses also includes types B, C [19] viruses; however, there is no evidence that type B, C, and D can infect avian species. The natural reservoir of influenza A viruses are avian species within the orders *Anseriformes* and *Charadriformes*. At least 16 of the 18 known haemagglutinin subtypes (H1-H16) and 9 of the known neuraminidase (N1-N9) subtypes have been identified in avian species [19]. Additionally, influenza A viruses can also infect different mammal species including humans, horses, pigs, cats, dogs, and even some marine mammals [6,43].

Furthermore, a new lineage of influenza A viruses have been recently identified in bats in Guatemala and Peru, suggesting the existence of other natural reservoirs of the virus. Nevertheless, the mechanisms that allow some influenza A viruses to cross the interspecies barrier are not clearly understood [2]. Influenza A viruses are pleomorphic, enveloped, and contain 8 genomic segments of negative- sense single strand RNAs (-ssRNA) [19]. The high genetic variability of this virus is the result of its mutagenic capacity (antigenic drift) and its potential to exchange genetic segments when two or more viruses infect the same cell (antigenic shift) [1]. These mechanisms of viral diversification have allowed the emergence of new variants, some with zoonotic and pandemic potential, hindering prevention, control, and treatment [43]. Additionally, these genetic changes may be associated with patterns of infection (e.g.

epidemic or pandemic) and the course of the disease (morbidity and mortality rates) [35].

From the pathogenic point of view, influenza A viruses in birds are classified as highly pathogenic (HPAI) or low pathogenic (LPAI) avian influenza viruses. To date, only the H5 and H7 subtypes have been proven to be HPAI viruses, although not all H5 and H7 viruses are HPAI viruses [1,2]. However, LPAI H5 or H7 viruses may become HPAI viruses due to mutations that occur after infection of poultry [2]. The presence of influenza viruses in poultry has serious repercussions on animal health, public health and trade of live poultry or poultry products. Due to some influenza a viruses are zoonotic and zoonotic influenza infections are a pandemic threat, all influenza a viruses found in poultry need to be notified to the World Organisation for Animal Health (OIE). It is estimated that HPAI viruses have greatly affected avian health and poultry production worldwide. More than 500 million poultry deaths have been associated with avian influenza infections [14] producing economic, political and/or socio cultural repercussions [41]. The influenza A viruses exist as several distinct subtypes, defined by the hemagglutinin (H) and neuraminidase (N) surface antigens, which infect humans and a range of avian and mammalian species. The influenza B viruses do not exhibit subtype variation and appear to infect humans only, causing epidemics but not pandemics—presumably because there is no reservoir of novel antigenic variation in nonhuman hosts. Influenza C viruses infect humans and have also been isolated from pigs in China, but these viruses are not associated with either epidemic or pandemic disease in the human population. The influenza A viruses exist in greatest profusion in waterfowl. At present, 15 distinct H and 9 distinct N antigenic types are recognized (Table 1), all of which occur in waterfowl in virtually all combinations. It is generally accepted that feral aquatic birds are the reservoir for influenza A viruses and that influenza in aquatic birds has achieved "evolutionary stasis" [2], meaning that the internal genes of the viruses show little genetic variation even over many decades, unlike those of the influenza viruses present in other species.

Global distribution of avian influenza subtypes

HPAIV H5N1 cumulative cases from 2003 to March 2012, as reported to OIE, were 2,655 in Viet Nam, 1,141 in Thailand, 1,084 in Egypt, 525 in Bangladesh, 273 in Romania,261 in Indonesia, 219 in Turkey, 149 in Russia, 114 in Myanmar, 112 in Korea, and 99 in China, including a total of 51 countries (OIE, 2012). Circulating H5N1 clades (1, 2.1.3, 2.2, 2.2.1, 2.3.2, 2.3.4 and 7) were examined for average within-group pair wise nucleotide distances, and found divergence greater than 1.5% within-group, indicating the need to split these groups into new order clades. Monophyletic groups of clade-specific trees resulted in the establishment of 12 new second, third-, and fourth-order clades. However, thirteen clades (0, 2.1.1, 2.1.2, 2.3.1, 2.3.3, 2.4, 2.6, 3, 4, 5, 6, 8, and 9) have not been detected since at least 2008. (Updated..., 2011). Avian outbreaks have been documented since the late 1950s, including A/chicken/Scotland/59, A/ tern/South Africa/61 and A/turkey/England/63 and the various H5N1 viruses, widespread since 2003 [35]. Global data on poultry imports, exotic bird trade and bird migrations were combined in an integrative analysis with phylogenetic data, identifying the possible pathway of 36 out of the 52 viral introductions. Spread through Asia and to Africa involved both migratory birds and poultry trade, and to Europe, mostly migratory birds (20 out of 23 countries). The North American risk was considered an association of the introduction of infected poultry, indicating the existence of illegal trade, with the North-South American bird travel dissemination [14]. In 2005, a new event occurred in the region of the Qinghai Lake nature reserve in the community of Gangcha, Qinghai Province, China, with mortality of natural reservoir species, especially the barred head goose, the brown and black head gull, ruddyshell ducks and great cormorant [15]. The isolate sequences of the HA, NA and NP genes were similar to those of the A/chicken/Shantou/4231/2003 (H5N1) gene, whereas other genes were similar to the A/chicken/Shantou/810/2005 (H5N1) strain found in Hong Kongin a peregrine falcon in 2004 and present in domestic chickens in 2005 [15]. In the middleof-2005, H5N1 strains derived from the isolates from Qinghai Lake Reservation, were found in Kazakhstan, Mongolia and Russia, and in 2006, these strains widespread across Southwestern and Central Europe, Africa and the Middle East [30]. An early warning system for HPAIV was established for surveillance in Alaska by the United States Geological Society. Sampling priority involves geographical areas used as corridors by migratory birds. The two main migratory routes monitored are East Asia-Australasian and East Asia-Southeast Asia-Arctic Siberia-Eastern Russia and Alaska. In the East Asia-Australasia route (20 countries), beach/shore birds of Russia, Siberian Arctic, Alaska and Southeast Asia, including North American islands of the Pacific, Australia and New Zealand are monitored for morbidity and mortality. Live wild birds killed by hunters, poultry sentinels or sentinel ducks placed in aquatic and terrestrial habitats are also under surveillance [39]. The frequency of exchange between AIV

clades or super families of Eurasia and America isolates of subtypes H1 to H13 and N1 to N9 were detected, but not of H14 and H15, in mallards of Alberta (Canada) and other birds, and seagulls in New Jersey (USA) between 2001 and 2006. HPAIV H5N1 strains were not detected in Eurasia and serological studies provided no confirmation of their movement into America. In North America, subtype H16 and an unusual cluster of H7N3, lethal to embryos, were found in beach birds and seagulls, but not in wild ducks. The results of 6,767 genetic analyses and 248 complete sequences suggested the lack of HPAIV H5N1 strains perpetuation in migratory birds and that its introduction from birds of Eurasia into America seems to be a rare event [16]. However, the relationship between epidemiological dynamics and genetic diversity patterns is not known at a continental scale [6]. The interface between migration routes in the northern hemisphere has allowed the exchange of infections, such as the transmission of AIV H2 into sea birds, from Asia to North America. Eurasian HA lineages were detected in North American AIV isolates, and considering that the 1957 pandemic was of the H2 sub-type, these data reinforce the need for continued surveillance [21].

Human-to-human transmission

Human-to-human transmission has been documented for H5N1 and H7N7 avian influenza viruses [3], and human-tohuman transmission of an H7N2 avian influenza virus may have occurred during a May 2007 outbreak in the United Kingdom. Human-to-human transmission of an H5N1 HPAI virus was first documented during the 1997 outbreak in Hong Kong, and subsequent instances of probable human-to-human transmission of H5N1 viruses have been reported from Thailand, Vietnam, Indonesia, and Pakistan [3]. Human-to-human transmission of highly pathogenic H7N7 virus was documented in conjunction with a widespread series of outbreaks of a highly pathogenic H7N7 virus among poultry farms in the Netherlands during March-May 2003, in which there was at least one human fatality from this virus among the 89 cases diagnosed at the time of the outbreak [13]. Subsequent serological investigations documented at least 33 instances of human-to-human transmission among the families of infected poultry workers, and estimated that at least 1000 individuals and possibly as many as 2000 people in the Netherlands were infected by the H7N7 virus over the course of the 2003 outbreak [4]. Epidemiological investigations were undertaken to determine whether human-to-human transmission of an H7N2 avian influenza virus occurred during an outbreak in the United Kingdom during May 2007 involving at least four confirmed human cases, three of whom were hospitalized for treatment prior to their diagnosis as human avian influenza cases [24].

Prevention and control

On April 27, 2007, the United States of America Food and Agriculture Administration (FDA) authorized the first HPAIV H5N1 vaccine to humans for the protection of groups at high risk (Skeika and Jabrb, 2008). The Food and Agriculture Organization of the United Nations published the list of the manufacturers of poultry influenza vaccines (FAO, 2012a). Vaccinations may reduce the risk of infection and lower virus output, with birds representing a lower sanitary risk, and may be used for poultry surrounding outbreaks zones. The three categories of strategies proposed for vaccination by FAO are: (1) Response to an outbreak, employing perifocal vaccination (*ring vaccination*) or vaccination only of domestic poultry at high risk, in combination with the destruction of infected domestic poultry; (2) Vaccination in response to a "trigger", upon the detection of the disease by surveillance studies, in areas where biosecurity is difficult to be implemented (e.g., high density of poultry farms); and (3) Pre-emptive baseline vaccination of chickens and other avian species when the risk of infection is high and/or the consequences of infection are very serious (FAO, 2012b).

After the influenza outbreaks in poultry and the potential pandemics threat to humans caused by the HPAIV of the H5N1 subtype, improvements in biosecurity and the use of inactivated vaccines are the two main options for the control of the disease. Vaccines against avian influenza are designed to induce the protection of flocks, preventing outbreaks, and can be used as tool in perifocal vaccinations to fight isolated episodes of the disease Although in the United States the control of the HPAIV was obtained by eradication programs, strategies were also employed against the velogenic and mesogenic strains of the Newcastle disease virus [40]. On April 27, 2007, the U.S. Food and Drug Administration (FDA) approved the first vaccine against HPAIV H5N1 for use in humans at high risk of infection [33]. A model plan for human influenza pandemics preparedness was published in Ireland. The essence of biosecurity is to minimize the risk of extraneous organisms from entering the premises where poultry are housed, and therefore it is the best strategy to reduce the risk of diseases in general, particularly when poultry are reared in confinement. Ideally, farms should be designed for biosecurity from the beginning. The costs of adaptation may be high and not very cost-effective, as changes in structures

Clinical sign of avian influenza

Clinical symptoms of avian influenza infections in humans range from asymptomatic infection or mild conjunctivitis to fatal systemic disease and multiorgan failure, including severe or fatal respiratory, gastrointestinal, or neurological syndromes [1]. Avian influenza infections in humans are believed to occur through virus contact and inoculation of the eyes, respiratory tract, and possibly the gastrointestinal tract: gastrointestinal infection by the H5N1 avian influenza viruses has been demonstrated in other species of mammals and is a normal route of infection in birds [32]. Although most human infections by avian influenza viruses are attributable to exposure to infected poultry, human infections resulting from exposure to avian influenza viruses from wild birds have been documented from Eurasia (H5N1: Azerbaijan), North America (H11N9: United States), and Africa (H10N7: Egypt) [31]. Although documented human infections with most avian influenza viruses have involved only conjunctivitis or only mild respiratory disease symptoms, fatal disease has been reported from persons infected with H5N1 and H7N7 viruses (Fouchier., *et al*. 2004, Beigel., *et al*. 2005). Human infections with the H5N1 virus are typically associated with pneumonia and other severe acute respiratory tract symptoms. Nonetheless, the clinical spectrum of H5N1 infections in humans is quite broad, and H5N1 virus has been recovered from many different body tissues, i.e., lung, brain, large intestine, small intestine, cerebrospinal fluid, kidney, spleen, liver, pharynx, blood, placenta, and the in-utero transmission of H5N1 from mother to fetus has also been reported [33]. Fatal atypical human H5N1 infections involving only gastrointestinal and neurological symptoms have been documented from patients in Vietnam and Thailand [7], and asymptomatic human infections with H5N1 have been reported from China, Vietnam, Japan, and Korea. Avian influenza infections have been reported from North America (H7N2) and China (H5N1) from individuals with no evident direct exposure to diseased birds or poultry [47]. No specific risk factors for human infection with the H5N1 virus other than exposure to sick and dead poultry or birds have been identified with absolute certainty [7], and it remains unclear why acute illness from H5N1 infections is so infrequently reported among poultry industry workers in countries where H5N1 outbreaks have been reported on commercial poultry farms [3]. Plucking and butchering of diseased poultry or wild birds, handling of fighting cocks, exposure to live poultry, consumption of uncooked duck's blood, and intimate contact with infected humans in household or hospital settings have been implicated as risk factors for human infection with the H5N1 virus [3]. Environmental exposure to poultry viruses through swimming or bathing in contaminated water, and exposure to poultry manure fertilizer, have been identified as possible risk factors for human infection with the H5N1 avian influenza virus [1]. Serological surveys conducted during an epidemiological investigation of the 1997 H5N1 outbreak in Hong Kong detected possible asymptomatic infections in 10 people. Confirmed asymptomatic H5N1 cases were identified in three people in Vietnam who were close relatives of confirmed H5N1 cases, and two animal attendants who had contact with infected tigers in Thailand. Serological studies have detected mild or asymptomatic H5N1 infections in five people involved in culling operations in Japan during 2004 [12], and among 10 poultry workers in Korea exposed to the H5N1 virus during outbreaks in 2003-2004 and 2006. The serologically confirmed human cases reported from H5N1 outbreaks in Japan and Korea are unusual in at leastwo respects: first, because all the recorded infections were from poultry workers or people involved in culls, and second, because all reported cases in these countries involved asymptomatic or only very mild clinical disease symptoms. Serological surveys have confirmed at least 13 human infections with an H5N2 virus in conjunction with outbreaks of a low pathogenic H5N2 on commercial poultry farms in Japan during 2005 [26].

Although most human infections with H7N7 viruses have involved conjunctivitis or mild respiratory symptoms, a fatal H7N7 case involving severe acute respiratory distress syndrome was reported from a veterinarian involved in culling operations during a widespread outbreak of an H7N7 virus in the Netherlands during 2003 [8]. Conjunctivitis was reported as the principal symptom for human H7N3 infections in the United Kingdom in 2006, and conjunctivitis and mild respiratory illness were reported for human H7N3 cases recorded in Canada during 2004 [38]. Human infections from an H9N2 virus have been recorded in Hong Kong and mainland China on several occasions since 1999, and involved patients who presented with nonfatal respiratory or influenza-like disease symptoms [18] Conjunctivitis and respiratory symptoms were reportedly exhibited by suspected human H7N2 cases during a May 2007 outbreak in the United Kingdom. Three of four confirmed human H7N2 cases from this outbreak reportedly exhibited respiratory disease symptoms, whereas one confirmed case was reportedly hospitalized for treatment of gastrointestinal and neurological symptoms the clinical presentation of AI in humans may be highly variable both between and within haemagglutinin subtypes. As with seasonal human influenza, a person infected with

AI may have no symptoms, mild upper respiratory symptoms, or symptoms typical of influenza (fever, cough, fatigue, myalgia, and sore throat, shortness of breath, runny nose, and headache); diarrhea may also occur (World Health Organization) [44].

Mild symptoms, including conjunctivitis and gastrointestinal symptoms, have been typically associated with several AI subtypes and should be considered in any person who has had close exposure to birds infected with any subtype of AI. World Health Organization, 2013An outbreak of LPAI H10N7 on a chicken farm in Australia was associated with conjunctivitis and mild respiratory symptoms in seven abattoir workers processing birds from this farm. H10 influenza subtype was laboratory confirmed in two of the cases [2]. A large outbreak of HPAI H7N7 in the Netherlands in 2004 was reported to have resulted in a rate of conjunctivitis of 8%, influenza like illness in 2%, and one death associated with respiratory failure in those exposed. The H5N1 subtype has caused viral pneumonia with a high case fatality rate, and in a small number of cases, diarrhoea, vomiting, abdominal pain, chest pain, and bleeding from the nose and gums have also been reported as early symptoms [44].

Avian influenza virus A(H5N1)

In 2017, highly pathogenic avian influenza A(H5N1) virus caused continued outbreaks and was detected in poultry and wild birds. Sporadic transmission to humans was observed in Egypt, with three reported cases, including one fatality, and in Indonesia, with one fatal case [WHO; 2018]. Transmission patterns were similar to previous years: cases were linked to close contact with infected poultry. Between 2003 and 2017, WHO reported 860 human cases of influenza A(H5N1), including 454 deaths [46].

A younger family member also died of a respiratory illness, but the aetiology was undetermined No new human cases due to AI A (H5N1) have been reported since the last report and within the reporting period. Since 2003 and as of 15 May 2018, 860 laboratory- confirmed cases of human infection with AI A (H5N1) virus, including 454 deaths, have been reported from 16 countries outside the EU/EEA. The latest case was reported in September 2017 by Indonesia (Figure 1 Source: Data from WHO) [15].

Figure 1 Distribution of confirmed human cases of A(H5N1) by country of reporting 2003-2018 (n = 860) Highly pathogenic avian influenza (HPAI) A (H5N1) virus, also known as 'Bird Flu', is responsible for sporadic cases of human infection. This virus was first detected in 2003. Since 2003, more than 600 human cases have been reported by WHO from 15 countries in Asia, Europe, the Pacific and the Near East. Case fatality rate of the infection is approximately 60%. Indonesia, Vietnam and Egypt have reported the highest number of human cases to date 9. HPAI H5N1 virus can infect the respiratory tract of humans. When people develop illness from HPAI H5N1 virus infection, severe respiratory illness (e.g. pneumonia and respiratory failure) and death may occur. The majority of HPAI H5N1 cases have occurred among children and adults younger than 40 years old. Mortality has been highest in people aged 10-19 years old and young adults. In the majority of cases, the person got HPAI H5N1 virus infection after direct or close contact with sick or dead infected poultry. Currently, there is limited evidence of human to human transmission of H5N1 infection. Some cases of limited, non-sustained human-to-human transmission have likely occurred. Seasonality of human cases of HPAI H5N1 has been observed with increases during months at the end and beginning of the year. This seasonality corresponds to the seasonality of HPAI H5N1 virus outbreaks among poultry, which increase during the relatively cooler periods. However, human cases can occur at any time, especially in countries where HPAI H5N1 is endemic in poultry. Currently, HPAI H5N1 virus is considered endemic in poultry in six countries (Bangladesh, China, Egypt, India, Indonesia, and Vietnam). However, many other countries have experienced poultry outbreaks 9 unlike influenza viruses that have achieved ongoing transmission in humans; the sporadic human infections with avian A (H5N1) viruses are far more severe with high mortality. Initial symptoms include a high fever and other influenza-like symptoms. Diarrhea, vomiting, abdominal pain, chest pain, and bleeding from the nose and gums have also been reported. Watery diarrhea without blood appears to be more common in H5N1 influenza than in normal seasonal influenza. The disease often manifests as a rapid progression of pneumonia with respiratory failure ensuing over several days. It also appears that the incubation period in humans may be longer for avian (H5N1) viruses, ranging from 2 to 8 days, and possibly as long as 17 days. As already noted, the HPAIV H5N1 strain was documented for the first time to have crossed the animal-to-human barrier in 1997, causing zoonotic fatal infections. By genetic analysis of the 1997 HPAIV H5N1, it was revealed that the six internal protein-encoding segments (PB2, PB1, PA, NP, M, NS) were derived from co-circulating avian H9N2 viruses [9]. The presence of the same set of segments in two human H9N2 isolates

in 1999 indicates an involvement of these segments in interspecies transmission [18]. Continuous evolution of the HPAIV H5N1 viruses that have undergone further multiple reassortments with other AIVs since 2003 was reported in several studies [20]. From January 2003 to May 2018, 860 human HPAIV H5N1 infections (including 454 fatalities) were reported worldwide. As evidenced by the low incidence rate compared to the H7N9 infections B(, H7N9), the risk of poultry-to-human transmission of HPAIV H5N1 strains is relatively low, but the case fatality rate (53%) is high. Due to their rapid evolution and genetic diversity, HPAIV H5N1 viruses were classified into first order clades (designated clades 0 to 9), which are further diversified into second, third or fourth order clades (e.g., 2.3, 2.3.4, 2.3.4.4) and sub-clades (e.g., 2.3.4.4b) according to their HA segment sequence [44] and genotypes [40] further diversified into second, third or fourth order clades (e.g., 2.3, 2.3.4, 2.3.4.4) and sub-clades (e.g., 2.3.4.4b) according to their HA segment sequence and genotypes. In 2003, clade 1 strains were first detected in northern Vietnam. Recently, clade 1 viruses are phylogenetically designated as clades 1.1.1 and 1.1.2. In 2005, clade 2.2 viruses were transmitted by wild birds from Qinghai Lake in western China to other Asian, European and African countries. Clade 2.2 has disappeared worldwide, except for Egypt, where in 2008 the virus became endemic in poultry and evolved into two distinct clades (e.g., 2.2.1.1 and 2.2.1.2). From March 2006 to May 2018, Egypt has reported a total of 359 cases, including 120 deaths. Since 2008 viruses evolved in China, Southeast Asia forming the new clade 2.3.2.1, which gained high prevalence, gradually replacing clade 1 viruses, and were also transmitted to Europe. Clade 2.3.2.1 continued its evolution resulting in new, genetically diverse sub-clades (2.3.2.1a, b and c) which are associated with sporadic, but fatal human infections in the last few years [6]. Currently, clade 2.3.2.1c viruses have become dominant in poultry throughout China, Cambodia, Laos, Indonesia, and Vietnam. Similar to the geographically restricted clade 2.2.1.2 in Egypt, endemic clade 2.1.3 viruses in Indonesia, recently evolved to the new clade 2.1.3.2b. Furthermore, viruses of clade 2.3.2.1c have been introduced to Indonesia, representing a challenge for the implemented strategies for diagnosis and control of HPAIV H5N1 viruses in this area. Currently, out of the more than 30 previously reported genetic clades, clades 1.1.2 (Cambodia and Vietnam), 2.1.3.2b (Indonesia), 2.2.1.2 (Egypt), 2.3.2.1c (Bangladesh, China, India, Indonesia, Korea, Nepal, and Vietnam), 2.3.4.2 (China), and 7.2 (China and Vietnam) are circulating in domestic poultry [7].

Avian influenza virus A (H5N6)

In 2017, China reported two human cases infected with avian influenza A(H5N6) virus, with the likely source of infection being exposure to infected poultry. No new human cases due to AI A(H5N6) have been reported since the last report and within the reporting period [12].

Figure 2 Number of human cases due to A(H5N6), clade 2.3.4.4, infection by year of onset, 2014-2018 (n = 19) HPAI A(H5N6) virus of clade 2.3.4.4 rom South Korea showed a higher pathogenicity and viral replication in the upper respiratory tract in ferrets than a HPAI A(H5N8) virus [13]. HPAI A(H5N6) was transmitted between ferrets through direct contact, whereas HPAI A(H5N8) did not transmit between ferrets. Both viruses had strong α-2,3 syliac acid receptor specificity with low α-2,6 syliac acid receptor specificity indicating an avian receptor preference. Unlike HPAI A(H5N8), the HPAI A(H5N6) virus had a NA stalk deletion and an 80 to 84 residue deletion in the NS1 gene. This study indicates a higher potential for HPAI A(H5N6) than for A(H5N8) to infect humans. Experiments with AI H5Nx viruses of clade 2.3.4.4 suggested that the lack of glycosylation could be involved in the induction of a T160A mutation in the HA protein, which exhibits binding to the α-2,3 and α-2,6 receptors [9].

In April 2014, the first fatal human infection with HPAI H5N6 was reported in China [31]. Patients acquired the infection through contact with infected poultry, particularly in live bird markets. The manifestation of the infection in humans ranged from influenza-like illness including fever and severe pneumonia to death. The genome of this strain was a combination of the HA segment from avian influenza A/H5N2 viruses (clade 2.3.4.4), the NA segment from avian influenza A/H6N6 viruses and internal protein encoding genes from avian influenza A/H5N1 viruses (clade 2.3.2.1c) [31]. To date, three different reassortants of HPAIV H5N6 crossed the species barrier and caused severe infections in human with high mortality rate. The strain "reassortant A-HPAIV H5N6" represents the prototypic HPAI H5N6 strain, which led to the first fatal H5N6 infection in humans. Independently, "reassortant B-HPAIV H5N6" concurrently resulted from reassortment between H5N8 (clade 2.3.4.4), and H6N6 viruses. Subsequently, the "reassortant B-HPAIV H5N6" was subjected to a single reassortment event by which it acquired the six internal genes of a co-circulating influenza A/H9N2 strain resulting in "reassortant C-HPAI H5N6" [47]. In November 2016, a

human fatality was associated with the isolation of H5N6 viruses, which originated in poultry after multiple reassortment events of several AIVs, including H3N2, H5Nx, H6N2, H7N3, and/or H9N2. This indicates the high zoonotic potential of these H5N6 viruses. From 2014 to May 2018, a total of 19 laboratory-confirmed human H5N6 infections (including six fatalities, case fatality rate = 32%) in China have been reported to WHO [44].

Avian influenza virus A(H7N4)

In December 2017, China reported the first human case infected with avian influenza A(H7N4) virus in a woman hospitalised with severe pneumonia. Before onset of disease, the patient had contact with live poultry in her backyard, which was also confirmed to be infected with A(H7N4) [44]. In February 2018, the Chinese National Health and Family Planning Commission (NHFPC) announced the first non-fatal human infection of H7N4 in Jiangsu Province. The patient was a 68-year-old woman who acquired the infection after exposure to poultry in a live bird market [44].

H6N1 (LPAIV)

Although the avian H6Nx viruses have shown the ability to productively infect and cause illness in mammalian model animals (mice and ferrets) without prior adaptation, the H6-type viruses were not detected in humans until May 2013 [10], when a human infection with LPAIV H6N1 was reported for the first time in Taiwan (Wei, S.H., *et al.* 2013). Coalescent-based phylogenetic analyses of the human influenza H6N1 strain showed that it was likely to be derived from different H6N1 strains and not by direct reassortment with the co-circulating AIV H5N2 [33]. Due to the high compatibility and the frequent reassortment between H5N2 and the internal genes of H6N1, there is a concern about the indirect contribution of H6N1-internal genes to trigger human infections when incorporated into the genetic backbone of American lineage influenza A/H5N2 viruses [18].

H7N2 and H7N3

First evidence of human infections with H7N2 (LPAIV) and H7N3 (LPAIV) was based on positive retrospective serologic analysis of workers involved in the poultry outbreaks in the United States (USA, Virginia) and Italy in 2002 and 2003, respectively [4]. The H7N2 (LPAIV) was then virologically reported in 2003 in an immune-compromised patient in the United States (New York, NY, USA), and later in 2007, it was detected in four human cases in the United Kingdom (Wales, UK). In addition, H7N3 (HPAIV/LPAIV) and H7N3 (LPAIV) led to sporadic human infections in 2004 and 2006 in Canada (British Columbia) and the UK (Norfolk), respectively). In 2012, two confirmed mild infections of humans with H7N3 (HPAIV) were detected following exposure to infected poultry in Mexico (Jalisco) [Centers for Disease Control and Prevention] [5].

H7N7

Mild human infections with HPAIVH7N7 "conjunctivitis" was reported in 1959, 1977, and 1981 [Belser, J.A., *et al*. 2009]. The most prominent human outbreak of HPAIV H7N7 occurred in the Netherlands in the spring of 2003 leading to 89 human cases including the first reported fatality due to HPAIV H7N7 infection [Koopmans, M.., *et al*. 2004, Van Kolfschooten, F. 2003]. The internal genes of this HPAIV H7N7 were of avian origin and were genetically related to the previously circulating LPAIV H7N7 in ducks in the same region in 2000 [Koopmans, M., *et al*. 2004]. In September 2013, three poultry workers in Italy were infected with H7N7 AIV. They acquired the infection after participation in culling of poultry infected with HPAIV H7N7. The patients had conjunctivitis. Genetic analyses of all gene segments indicated high similarity to the H7N7 viruses isolated from chickens on affected farms. In 2013, a previously unrecognized low pathogenic H7N7 lineage carrying the complete set of internal genes from H9N2 subtype AIV was detected in chickens in China and has the ability to infect mammals experimentally [17].

Avian influenza virus A(H7N9)

After the identification of a novel reassortant low pathogenic avian influenza virus A(H7N9) in China in March 2013, which has since mutated into a highly pathogenic form for poultry, 1 566 human cases, including 613 deaths, were reported from China, Hong Kong Special Administrative Region (SAR) and Taiwan, while Canada and Malaysia had previously reported travel-related cases [44]. In 2017, WHO reported 600 laboratory-confirmed human cases due to avian influenza A(H7N9) viruses, including at least 248 deaths (41%) [28]. The main sources of infection were exposure to infected poultry or contaminated environments. No sustained human-to-human transmission has been recorded, although clusters of human cases were identified. In March 2013, China first reported human infections with a novel avian influenza A (H7N9). It is a serotype of 'Influenza A' virus (RNA virus from 'Orthomyxoviridae' family).H7N9 infection is hosted by birds, pigs, dogs and human as well. Though some mild illnesses in human H7N9 cases

have been seen, most patients had exhibited severe respiratory illness, with about one-third resulting in death. Close contacts with infected poultry or contaminated environment considered to be the mode of transmission of the virus. However, recent study shows the evidence of airborne exposure too. No evidence of sustained person-to-person spread of H7N9 has been found, though in rare circumstances some evidence indicates to limited person-to-person spread 4. No cases of H7N9 outside of China have been reported yet. A case has been detected in Taiwan; however, the patient has a recent travel history to affected area of China. China has acted very efficiently to control the recent H7N9 outbreak. Though the last outbreak of H7N9 did not cause a pandemic, a case has crossed international borders. The most concerning in this situation is that if there is another H7N9 outbreak, the infection might end up as a pandemic the result of which can be catastrophic. Influenza viruses constantly change their genetic properties. It is possible that during this process a virus could gain the ability to spread easily and sustainable among people, triggering a global outbreak of disease (pandemic). International health agencies like WHO, CDC are following this situation closely and coordinating with domestic and international partners.

In 2013, zoonotic infections with LPAIV H7N9 were first reported in China. The human pathogenic H7N9 is derived from multiple reassortments between AIV H7N9 (NA), H7N7 (HA), and H9N2 (internal proteins coding gene segments) in domestic ducks and chickens [17]. The virus is still maintained in poultry leading only to sporadic human infections. In February 2017, the Chinese province Guangdong reported the first human infection with the mutated trypsin-independent HPAIV H7N9 [13]. Recent studies revealed that the newly emerging HPAIV H7N9 viruses acquired the internal protein-coding genes from co-circulating H9N2 strains [47]. Despite the higher viral polymerase activity, increased replication efficiency and pathogenicity in human, no clear impact on viral transmissibility or virulence was noticed for HPAIV H7N9. From February 2013 to July 2018, there were a total of 1625 human infections (LPAIV H7N9: 1593 cases, HPAIV H7N9: 32 cases) in China, Malaysia (one case, imported from China) and Canada (two cases, imported from China) with an average of 295 cases per year. The infections caused a total of 623 fatalities (38% case fatality rate]. Since 2013, six waves of LPAIV and HPAIV H7N9 were documented. No additional human cases have been reported since the last report in March 2018 [44].

The total number of human cases since February 2013 remains at 1,567, all outside of Europe, including 569 with fatal outcome; see figure 3 and table 1). According to the Chinese National Influenza Center (2018), 32 human cases have been infected with HPAI A (H7N9) (Source: Data from WHO. A report of a patient infected with HPAI A (H7N9) in Shaanxi, China in May 2017 supported the notion of a westward spread of the infection as well as the key role of poultry trade in driving the geographic distribution of the virus [47]. The influence of weather conditions was investigated for the time period 2013-2016 [18]. The risk of infection increased on cold-dry days with risk-associated temperatures and vapour pressures differing between the north (0-18C, 313mb) and south of China (7-21C, 3-17mb).

The genetic diversity of A(H7N9) viruses in China increased after emergence and during the first three waves but decreased in the recent waves indicating a more stable situation. It was during these more recent waves, however, that most human infections occurred, possibly due at least in part to differences in gene composition. Genetic variability has also been observed in human patients infected with A(H7N9) viruses [48]. However, it is not fully understood how high polymorphism and variation within different viral genes contributed to disease progression and severity overall. A recurrent study describes a potential family cluster of A (H7N9) infection in China in 2016 [41]. A likely transmission occurred from the father to his daughter through close contact. Virological analyses identified nearly identical sequence data with three amino acid mutations in the HA protein that might have increased the binding affinity for the human receptor. A retrospective study of hospitalized patients infected with A (H7N9) between 2013 and 2017 looked at the impact of treatment with neuraminidase inhibitors on virus shedding showed that RNA shedding was shorter in survivors than patients with fatal outcome [41].

Avian influenza virus A(H9N2)

In 2017, China reported six human cases due to avian influenza A(H9N2) virus. All six were exposed to poultry before onset of symptoms. Since 1998 and as of 15 May 2018, 46 laboratory-confirmed cases of human infection with AI A(H9N2) virus, including one death, have been reported globally. These are three additional cases than those reported in the previous report (EFSA., *et al*. 2018). Cases occurred in China [39], Egypt [3] and Bangladesh [3] (Figure). The latest case was reported in February 2018 from China. Since the mid-1980s, the LPAIV H9N2 circulates extensively worldwide in poultry resulting in high genetic diversity [18]. Based on phylogenetic analysis of the HA segment sequence, H9N2 viruses are designated either as Eurasian or American lineages [9].

Since the mid-1990s, the BJ/94-, G9-, and G1-like H9N2 viruses are predominantly circulating in chickens and quails in China. Since 2010, the G1-like lineage demonstrated a widespread distribution and prevalence throughout Asia, the Middle East, North Africa,

and Europe [22]. The seroprevalence for G9- and G1-like H9N2 antibodies among occupationally exposed populations in Southern China emphasized the high incidence rate of subclinical human infections with both prevalent H9N2 lineages. Moreover, in different geographical locations, H9N2 IAVs have crossed the species barrier due to their mammalian-like characteristics, causing mild to moderate infections [24,42]. Globally, since March 2013, a total of 27 laboratory confirmed human clinical infections were reported in three hotspots of human AIV infections (21 cases in China, 4 cases in Egypt, and 2 cases in Bangladesh). Currently, the global concern about H9N2 viruses is associated with their ability to donate their genes to other AIV giving rise to high and low pathogenic IAVs that could cross species barriers and infect humans. In addition to the zoonotic H5N6, H7N9 and H10N8 AIV, the H9N2 viruses also donated their internal genes to other IAVs, such as avian H5N1 [7].

H10N7 (LPAIV)

Although outbreaks of H10N7 are uncommon, this virus can sporadically cross the species barrier to mammals including humans. Human infections with H10N7 were occasionally reported from Egypt (2004) and Australia (2010). Recent H10N7 AIV-associated natural outbreaks in harbor seals and experimental infection of ferrets emphasize that H10N7 may possess a zoonotic potential [40].

H10N8 (LPAIV)

In late 2013, a fatal human infection with LPAIV H10N8 was identified in China [Chen, H., *et al*., 2014]. Notably, the human H10N8 IAV isolate possessed genes coding for internal proteins, which were genetically related to the contemporary AIV H9N2 strains [6]. suggesting that this unique genetic constellation was established in poultry. Non-fatal human infections with H10N7 IAV were previously reported in 2004 and 2010 at other geographical localities (reviewed in) [34].

Influenza A/H5N1

Year	Place	Virus sub type	Infection (death)	Symptoms
1995	UK	H7N7	1	Conjunctivitis
1997	Hong Kong	H5N1	18(6)	Respiratory
1999	Hong Kong	H9N2	2	Respiratory
2003	Hong Kong, Netherland	H5N1, H7N7, H9N2	2(1), 83,1	Respiratory
2004	Canada	H7N3	2	Conjunctivitis 1, respiratory 1
2004 - 2006	Vietnam, Thailand	H5N1	93(42), 22(14)	Respiratory
2005 - 2006	Cambodia, Indonesia and China	H5N1	4(4), 29(22)	Respiratory
2006	Tukey, Iraq	H5N1	15(10), 12(4), 2(2)	Respiratory

Table 1: Confirmed cases of avian-to-human transmission of influenza A subtypes [27,53].

http://www.who.int/csr/disease/avian_influenza.

On the basis of antigenic and genetic analyses of influenza virus isolates from migratory ducks, domestic ducks, pigs, and humans and experimental infection studies of birds and mammals with those viruses, the OIE Reference Laboratory proposed that the hemagglutinin (HA) gene of A/Hong Kong/68 (H3N2) strain was introduced into the precedent human H2N2 Asian influenza virus by genetic reassortment, that occurred in the epithelial cells lining the upper respiratory tract of pigs, through domestic ducks from an H3 influenza virus circulating in migratory ducks in southern China [15]. Both influenza A and B viruses cause seasonal epidemics each year, with 3 to 5 million infections and 250,000 to 500,000 deaths worldwide. Over 200,000 hospitalizations and 30,000 to 50,000 deaths are attributed to seasonal influenza infection in the United States annually. Some groups, including the elderly, infants, children under 5 years old, pregnant women, and people with chronic diseases, are at high risk of influenza infection with increased mortality rates. In addition to annual seasonal outbreaks, influenza pandemics also occur occasionally. In the past 200 years, there have been five pandemics: the 1918 H1N1 Spanish flu pandemic, the 1957 H2N2 Asian pandemic, the 1968 H3N2 Hong Kong pandemic, the 1977 H1N1 pandemic, and the 2009 H1N1 pandemic [36]. From 2003 to 2017, the World Health Organization (WHO) reported that 453 cases of deaths happened in a total of 858 confirmed human cases of H5N1 infection, which indicated that H5N1 HPAI leads to more than 50% mortality in humans. In addition, some avian H7 and H9 subtypes, such as H9N2 LPAI (low pathogenic avian influenza), H7N7 HPAI, and H7N3 HPAI, have been reported to cause human infections [2].

Human infections due to A(H5N6)

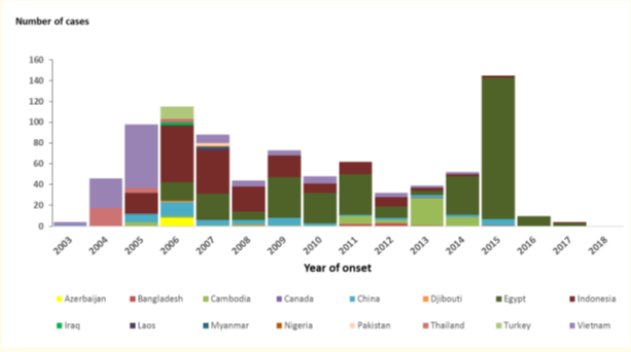

Figure 1: Distribution of confirmed human cases of A(H5N1) by country of reporting 2003 - 2018 (n = 860).

Source: Data from WHO [44].

Human infections due to A(H5N1)

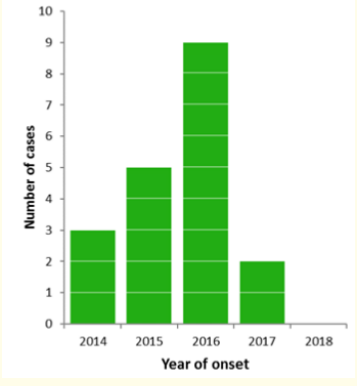

Figure 2: Number of human cases due to A(H5N6), clade 2.3.4.4, infection by year of onset, 2014-2018 (n = 19) HPAI A(H5N6) virus of clade 2.3.4.4 from South Korea showed a higher pathogenicity and viral replication in the upper respiratory tract in ferrets than a HPAI A(H5N8) virus [15]. HPAI A(H5N6) was transmitted between ferrets through direct contact, whereas HPAI A(H5N8) did not transmit between ferrets. Both viruses had strong α-2,3 syliac acid receptor specificity with low α-2,6 syliac acid receptor specificity indicating an avian receptor preference. Unlike HPAI A(H5N8), the HPAI A(H5N6) virus had a NA stalk deletion and an 80 to 84 residue deletion in the NS1 gene. This study indicates a higher potential for HPAI A(H5N6) than for A(H5N8) to infect humans. Experiments with AI H5Nx viruses of clade 2.3.4.4 suggested that the lack of glycosylation could be involved in the induction of a T160A mutation in the HA protein, which exhibits binding to the α-2,3 and α-2,6 receptors [9].

Human infections due to A(H7N9)

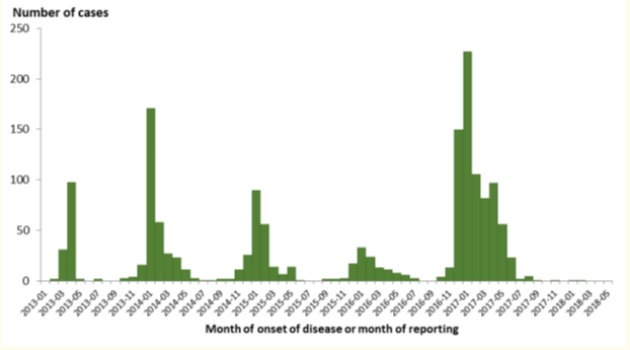

Figure 3: Distribution of confirmed human cases of A(H7N9) by month of onset of disease or month of reporting, February 2013-15 May 2018 (n= 1 567).

Source: Data from WHO [44].

Signs and symptoms of avian influenza a virus infections in humans

Signs and symptoms may depend on which avian influenza A virus caused the infection.

Low pathogenic avian influenza (LPAI) A virus infections of humans have been associated with generally mild, non-fatal illness. The reported signs and symptoms of LPAI A virus infections in humans have ranged from conjunctivitis to influenza-like illness (e.g., fever, cough, sore throat, muscle aches) to lower respiratory disease (pneumonia) requiring hospitalization. On the other hand, highly pathogenic avian influenza (HPAI) A virus infections of humans have been associated with a wide range of illness. Illness has ranged from conjunctivitis only, to influenza-like illness, to severe respiratory illness (e.g. shortness of breath, difficulty breathing, pneumonia, acute respiratory distress, viral pneumonia, respiratory failure) with multi-organ disease, sometimes accompanied by nausea, abdominal pain, diarrhea, vomiting and sometimes neurologic changes (altered mental status, seizures). Sometimes infection with highly pathogenic avian influenza A virus infection leads to death, especially with HPAI H5N1 virus [11]. The precision of clinical diagnosis of human infection with avian influenza A viruses on the basis of signs and symptoms alone is limited because symptoms from illness can be caused by other pathogens, such as Respiratory syncytial virus, Pneumococcus including seasonal influenza A or B viruses, can overlap considerably.

Detecting avian influenza a virus infection in humans

Avian influenza A virus infection in humans cannot be diagnosed by clinical signs and symptoms alone; laboratory testing is required. Avian influenza A virus infection is usually diagnosed by collecting a swab from the nose or throat of the sick person during the first few days of illness. In some cases, specimen from lower respiratory tract is also done. This specimen is sent to a lab; the laboratory looks for avian influenza A virus either by using a molecular test, by trying to grow the virus, or both [11]. In Bangladesh, usually Rrtpcr method is used to diagnose the infections. Viral isolation facility is also available. Treatment of Avian Influenza A Virus Infections in Humans CDC and WHO currently recommend Neuraminidase inhibitors such as Oseltamivir or Zanamivir, for treatment and prevention of human infection with avian influenza A viruses.

Prevention of human infection with avian influenza a viruses

The best way to prevent infection with avian influenza A viruses is to avoid sources of exposure i.e. direct or close contact with infected poultry. As there are evidence of rare episodes of limited, non-sustained human-to human transmission of HPAI H5N1 virus, persons should avoid sick patients who have suspected or confirmed HPAI H5N1 virus infection. Frequent hand wash with soap water and maintenance of hygiene practices can prevent influenza virus infection. Seasonal influenza vaccination will not prevent infection with avian influenza A viruses, but can reduce the risk of co-infection with human and avian influenza A viruses [11]. Health care personnel caring for patients with suspected or confirmed HPAI H5N1 virus infection should wear recommended personal protective equipment and follow recommended infection control measures (standard, droplet, contact, and airborne precautions.

Prevention and control

On April 27, 2007, the United States of America Food and Agriculture Administration (FDA) authorized the first HPAIV H5N1 vaccine to humans for the protection of groups at high risk (Skeika and Jabrb, 2008). The Food and Agriculture Organization of the United Nations published the list of the manufacturers of poultry influenza vaccines [28]. Vaccinations may reduce the risk of infection and lower virus output, with birds representing a lower sanitary risk, and may be used for poultry surrounding outbreaks zones. The three categories of strategies proposed for vaccination by FAO are: (1) Response to an outbreak, employing perifocal vaccination (ring vaccination) or vaccination only of domestic poultry at high risk, incombination with the destruction of infected domestic poultry; (2) Vaccination in response to a "trigger", upon the detection of the disease by surveillance studies, in areas where biosecurity is difficult to be implemented (e.g., high density of poultry farms); and (3) Pre-emptive baseline vaccination of chickens and other avian species when the risk of infection is high and/or the consequences of infection are very serious. After the influenza outbreaks in poultry and the potential pandemics threat to humans caused by the HPAIV of the H5N1 subtype, improvements in biosecurity and the use of inactivated vaccines are the two main options for the control of the disease. Vaccines against avian influenza are designed to induce the protection of flocks, preventing outbreaks, and can be used as tool in perifocal vaccinations to fight isolated episodes of the disease Although in the United States the control of the HPAIV was obtained by eradication programs, strategies were also employed against the velogenic and mesogenic strains of the Newcastle disease virus [40]. On April 27, 2007, the U.S. Food and Drug Administration (FDA) approved the first vaccine against HPAIV H5N1 for use in humans at high risk of infection [34].

The 2009 H1N1 pandemic in United States resulted in approximately 43 million to 89 million cases, 195,000 to 403,000 hospitalizations, and 8,900 to 18,300 deaths, including 910 to 1,880 deaths among children. The pH1N1 influenza virus contained a combination of gene segments that had not been previously reported in animals or humans. The early serologic data suggested that many older adults had some cross-reactive immunity to the pH1N1 due to prior infection with antigenically related strains, while children and most young adults were immunologically naive. In the United States, the pandemic was characterized by two distinct waves: first, April through July 2009, and the second, from August 2009 to February 2010. Within 1 week of the recognition of the nation's first case, 10 cases had been confirmed in 3 states signaling onset of a first wave. Consistent with early serological data, the majority of reported cases were in people <= 24 years of age, and only 1 % of cases were in individuals >=65 years of age. The signs and symptoms reported among the pH1N1 cases were similar to those observed in patients with seasonal influenza, with the exception of diarrhea which was more common in pandemic patients. Unlike seasonal influenza when hospitalizations are more common among persons over 65 years of age, the majority (>70%) of pH1N1 hospitalizations were in people younger than 50 years of age, with hospitalization rates highest in 0-4-year-old group. The majority of adults and children hospitalized with pH1N1 infec-

tions had at least 1 underlying medical condition, and 20-25% of all hospitalized people required intensive care unit (ICU) admission. The age distribution of laboratory-confirmed pH1N1 influenza-associated death rate was also markedly different from that seen in typical influenza seasons. In contrast to typical influenza seasons, when 90% of deaths occur in the elderly population, over 80% of reported pH1N1 deaths were in persons younger than 65 years of age. Reported pediatric deaths from the pH1N1 were almost 4 times higher compared to death rate during the seasonal influenza. Pregnant women were more than 4 times more likely to be hospitalized with pH1N1; estimated 5.8% of all deaths from pH1N1 were in pregnant women even though they comprise only 1% of the total population. Epidemiological studies indicated that the virus was at the low end of transmissibility, compared with the strains that caused the 1918 pandemic, and was comparable to or slightly less transmissible than the strains that caused the 1957 and 1968 pandemics. On average, there were 1.5 secondary cases per one person with pH1N1. The CDC estimated that, from April 2009 through March 2010, pH1N1 virus was associated with about 60 million cases, 270,000 hospitalizations, and 12,270 deaths in the United States. This estimate represents a cumulative pH1N1 attack rate in the United States of approximately 20%. In conclusion, the H1N1 pandemic experience showed that disease estimates were substantially lower than envisioned in the pandemic preparedness planning assumptions.

Highly versus low pathogenic avian influenza viruses (HPAIV vs. LPAIV)

AIV are typed according to their pathogenicity in chickens into low pathogenic (LP) and highly pathogenic (HP) strains. LPAIVs are maintained in wild aquatic birds almost without developing severe clinical signs of the disease. The clinical signs in domestic poultry induced by LPAIVs include a body weight reduction and/or a slight drop in egg production in layers poultry. In contrast to LPAIV, the HPAIV phenotype is restricted to H5Nx, H7Nx, and H9N2 subtypes that carry a multi basic cleavage site in their HA and cause up to 100% mortality in several bird species [2].

Until the mid-1950s, all HPAIVs were characterized as H7-subtypes, while, in 1959, the first outbreak with HPAIV H5N1 in chickens was reported. Except for the fatal outbreak in terns caused by HPAIV H5N3 in South Africa, the HPAIV outbreaks were only reported in flocks of domestic birds until 2002. Since that time, HPAIVs were frequently reported to cause fatal outbreaks in wild aquatic and terrestrial birds [6].

Evolution and Epidemiology of IAV

IAV evolve mainly by two mechanisms: (1) through accumulation of point mutations due to the lack of a proof-reading function of the RdRp, leading to aa changes (referred to as antigenic drift) (Figure 3A) and (2) by reassortment of viral segments from different IAV during co-infection (referred to as antigenic shift) (Figure 3B). Interestingly, the point mutation rate is higher in human than in avian IAV [25]. In addition, a slower evolution rate has been observed in IAV isolated from wild aquatic birds compared with those from terrestrial poultry, swine or humans. This is probably due to adaptation of IAV to new hosts, while genetic stasis is maintained in its natural reservoir [8]. Additionally, reassortment was only reported to take place within each influenza virus genus (A, B, and C), but has not been observed among different genera. Genetic reassortment and antigenic drift, resulted in 5 documented influenza pandemics since 1900 and in annually repeated seasonal epidemics, respectively [20]. Unlike epidemics, pandemics can spread over a wide geographic area in relatively short time resulting in thousands or even millions of fatal infections. The notorious Spanish influenza (H1N1) led to the most dramatic pandemic of the last century, globally killing more than 25 million people in 25 weeks between 1918/1919. Subsequently, a new pandemic strain—Asian Flu (H2N2)—a reassortant of 1918/H1N1 and the HA/NA/PB1 segments of an AIV, emerged in China in 1957 leading to at least one million fatalities. In 1968, the pandemic Hong Kong Flu (H3N2), a reassortant of the 1957/H2N2 and HA/PB1 segments from another avian IAV, emerged to replace the older H2N2 strain and led to about one million deaths. In 1977, Russian influenza, which is thought to be caused by a re-emerged H1N1 virus, spread worldwide, leading to severe infections in humans with a 50% fatality rate among school-aged children [26]. In 2009, a reassortant H1N1 (H1N1pdm09) virus with a unique genome constellation generated in swine led to the first pandemic of the current century, known as "Swine Flu." The PB2 and PA segments were derived from a North American AIV, the PB1 segment from a human H3N2 virus, the NA and M segments from an Eurasian avian-like swine virus, and the HA, NP, NS segments from the H1N1-type classical swine virus [11]. Unlike H2N2, the H3N2 and H1N1 viruses are still circulating in the human population together with IBV strains [3]. In March 2018, a seasonal reassortant IAV-subtype H1N2 with ge-

nome segments from seasonal H1N1pdm09 (HA and NS) and H3N2 (PB2, PB1, PA, NP, NA and M) was identified in a 19-months old patient with influenza-like illness in the Netherlands [23]. However, epidemiological and virological investigation did not reveal additional human infections with this H1N2-subtype in the same region. Since 2013, new reassortant AIVs (e.g., H5N6, H6N1, H7N4, H7N7, H7N9, H9N2, H10N8) have crossed the species barrier to infect humans inducing asymptomatic to fatal infections [42]. Remarkably, breaking the host barrier was mostly supported by the acquisition of gene segment(s) from other cocirculating AIVs, especially H9N2 [17].

Avian influenza or bird flu is a highly contagious acute viral disease that can occur in epidemics and cross-border forms in poultry. Influenza A viruses are the aetiological agent of avian influenza and belong to the *Orthomyxoviridae* family. Influenza viruses also includes types B, C [19] viruses; however, there is no evidence that type B, C, and D can infect avian species [43]. The natural reservoir of influenza A viruses are avian species within the orders *Anseriformes* and *Charadriformes*. At least 16 of the 18 known haemagglutinin subtypes (H1-H16) and 9 of the known neuraminidase (N1-N9) subtypes have been identified in avian species [19]. Additionally, influenza A viruses can also infect different mammal species including humans, horses, pigs, cats, dogs, and even some marine mammals [43]. Furthermore, a new lineage of influenza A viruses have been recently identified in bats in Guatemala and Peru [36], suggesting the existence of other natural reservoirs of the virus. Nevertheless, the mechanisms that allow some influenza A viruses to cross the interspecies barrier are not clearly understood [2]. Influenza A viruses are pleomorphic, enveloped, and contain 8 genomic segments of negative- sense single strand RNAs (-ssRNA) [19]. The high genetic variability of this virus is the result of its mutagenic capacity (antigenic drift) and its potential to exchange genetic segments when two or more viruses infect the same cell (antigenic shift). These mechanisms of viral diversification have allowed the emergence of new variants, some with zoonotic and pandemic potential, hindering prevention, control, and treatment [43].

Conclusion

There are two main types of influenza, influenza A and influenza B. Influenza A viruses are divided into subtypes based on the hemagglutinin (H) and neuraminidase (N) proteins on their surfaces. Influenza A viruses infecting humans have been primarily subtypes H1, H2, and H3 while influenza A subtypes H1 through H17 can infect birds and other animals such as pigs. There are in addition ten different neuraminidase surface proteins. Reservoirs for influenza A viruses include humans, swine, poultry and other birds and mammals. Humans are the primary reservoir for influenza B. Seasonal influenza viruses spread person-to-person primarily through large-particle respiratory droplet transmission (e.g., when an infected person coughs or sneezes near a susceptible person). Transmission via large-particle droplets requires close proximity between source and recipient persons because droplets do not remain suspended in the air and generally travel only a short distance (<6 feet). Other possible routes of influenza transmission are mucosal inoculation from hands touching contaminated surfaces and airborne transmission. The relative contribution of each type of transmission has not been defined but for airborne transmission is thought to be small. Avian and swine influenza viruses are generally less transmissible from person-to-person than seasonal influenza viruses. These viruses are primarily transmitted from animals to humans directly or through environmental contamination. However, limited person-to-person transmission has been described with these viruses.

Recommendation

- Cover your nose and mouth with a tissue when you cough or sneeze. Throw the tissue in the trash after you use it and then clean your hands;
- Wash your hands with soap and water frequently, especially after you cough or sneeze. Alcohol-based hand cleaners are also effective;
- Try to avoid close contact with people ill with respiratory symptoms;
- If you get sick with respiratory symptoms, stay home the recommended period and limit contact with others to keep from infecting them;
- Avoid touching your eyes, nose or mouth;
- Don a mask when entering a healthcare facility if you are coughing or sneezing.

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