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Avian influenza H5N1: still a pandemic threat?

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Abstract. Highly pathogenic avian influenza H5N1 viruses have become endemic in global poultry populations over the past 25 years and pose an ongoing public health threat. Although the incidence of human cases has declined, viruses from the H5N1 lineage can now be found in poultry throughout Asia, the Middle East and Africa, in addition to causing outbreaks in Europe and the Americas. The recent emergence and spread of reassortant H5Nx viruses, resulting in regional poultry outbreaks, has increased the risk for further evolution of these viruses and possible avian-to-human transmission. Ongoing surveillance and pandemic preparedness for H5N1 and other avian influenza viruses of public health concern are warranted.

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Introduction

Influenza A viruses are one of the most important human pathogens. Since the start of the 20th century, these viruses have been responsible for four pandemics in the human population, including the 1918 H1N1 'Spanish flu' pandemic that resulted in the deaths of over 50 million people[1]. Subsequent influenza pandemics also occurred in 1957 (H2N2, 'Asian flu'), 1968 (H3N2, 'Hong Kong flu') and 2009 (H1N1, 'Swine flu')[2,3]. Following the pandemic period of spread (usually 2–3 years), the virus typically takes on a seasonal pattern of circulation. Currently, the two seasonal influenza viruses circulating in humans emerged during the pandemics in 1968 (H3N2) and 2009 (H1N1).

The natural reservoir of influenza A viruses (known as avian influenza viruses, AIVs), are wild waterbirds from the Orders Anseriformes (ducks, geese, swans) and Charadriiformes (waders, gulls, terns)[4]. There is a large diversity of AIVs amongst their natural avian reservoirs. These viruses replicate in the gastrointestinal tract of their avian hosts which shed large quantities of virus into their aquatic environment. AIV infections in wild waterbirds are generally asymptomatic, or cause mild infections, enabling birds to carry viruses over vast distances during seasonal migrations[5]. AIVs can jump the species gap from their natural hosts to a wide range of avian and mammalian (e.g. humans, pigs, horses, dogs, cetaceans) hosts (Figure 1). In the context of human exposure risk, the most important of these secondary hosts are domestic poultry and pigs.

Avian influenza ecology

The poultry industry makes important contributions to nutrition, food security and family income in resource-limited settings[6]. Although some countries have recently made the transition to intensive farming with improved biosecurity practices, in many settings birds are raised in subsistence-level backyard or village farms. In these settings, large flocks of birds are allowed to roam free where there is ample opportunity for them to interact with wild waterbirds or the contaminated aquatic environment, thus introducing AIVs into poultry circulation. Excess birds are commonly transported to central live bird markets (LBMs) where they are sold to consumers and slaughtered by the vendor at the market. LBMs have been associated with avian influenza persistence, distribution and the potential emergence of novel viruses[7]. The presence of multiple avian species, the lack of sufficient biosecurity measures and the constant introduction of immunologically naïve animals contribute to the threat of the emergence of novel influenza strains with pandemic potential (Figure 2). High levels of avian influenza viruses of public health concern (e.g. H5N1, H7N9, H9N2) have been detected in LBMs throughout Asia, the Middle East and Africa through longitudinal surveillance initiatives[8–12]. Indeed, many human cases of AIV infection have been associated with contact with poultry at LBMs[13,14].

Avian influenza evolution

AIVs can be classified into low pathogenic avian influenza viruses (LPAIVs) and highly pathogenic avian influenza avian influenza viruses (HPAIVs), based on their virulence in domestic chickens[15]. Both LPAIVs and HPAIVs can cross the species gap to infect humans, but adaptation to the new host is required before the virus will be able to spread efficiently amongst this new host. AIVs can evolve this ability through two main mechanisms: (1) due to the segmented RNA genome of AIVs, when two different viruses infect an individual animal at the same time reassortment can occur between the genetic material, potentially resulting in progeny viruses that have the ability to spread in the human population (this process

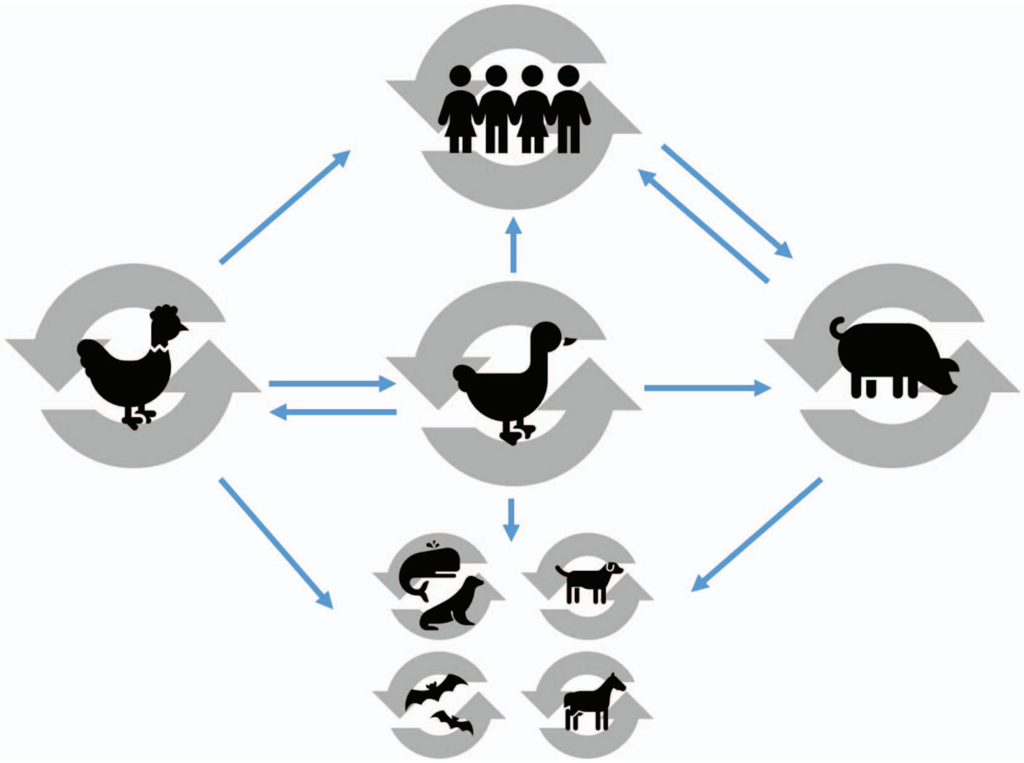

Figure 1. Schematic diagram of avian influenza virus reservoirs and interspecies transmission. Movement of viruses between species is indicated by arrows. Arrow-circles indicate sustained circulation of influenza viruses occurs in these hosts.

Figure 2. The constant introduction of multiple avian species into live bird markets from different sources promotes avian influenza persistence and drives the emergence of novel reassortant strains.

is called antigenic shift); and (2) the high mutation rate of AIVs during replication can lead to the accumulation of mutations that result in an AIV strain that is better adapted to the new host (this process is called antigenic drift)[16–18].

A/H5N1 emergence and human cases

Influenza H5N1 emerged as a public health threat in 1997, following the detection of human infections associated with poultry exposure in Hong Kong LBMs. During this outbreak, 18 cases of H5N1 human infection were detected in Hong Kong with a case fatality rate (CFR) of 33%[19]. The outbreak was contained when Hong Kong authorities closed LBMs and conducted mass culling of poultry[19]. Unfortunately, the virus subsequently re-emerged in China in 2003, and rapidly spread throughout Southeast Asia during 2004–2005[20]. Poultry outbreaks of influenza A/H5N1 virus have now been reported from many countries in Asia, Europe, the Middle East and Africa[21,22]. The global spread of H5N1 has been facilitated by the migration of wild waterbirds, the natural host for AIVs. To date, 17 countries have reported human H5N1 infections, with more than 860 confirmed human cases and a CFR of ~53%[23]. Over the ~25 years since A/H5N1 first emerged, the virus has diversified into multiple HA clades and subclades. Some of these strains have displayed greater fitness for spreading amongst poultry and others have been associated with a higher risk of human infection and disease[24,25].

Current influenza A/H5 circulation

Human H5N1 cases peaked in 2005–2007, followed by a steady decline in cases over the following 15 years, including only one case over the last four years (Figure 3). An obvious break in this trend occurred in 2015 when the emergence of a new strain in Egypt (clade 2.2.1.2), led to an upsurge in human H5N1 cases[26]. A similar (but not as dramatic) increase in cases occurred in Cambodia in 2013-2014, also linked with the emergence of a new strain (clade 1.1.2 reassortant)[27]. These cases highlight that although human infections with H5N1 are currently very low this situation can rapidly change following the emergence of novel strains through viral mutations. Indeed, there has been a recent emergence and spread of HPAIV H5 viruses (predominantly clade 2.3.4.4) that have undergone reassortment with various LPAIVs to give rise to a group of viruses known as H5Nx[28]. The clade 2.3.4.4 H5Nx lineage of viruses first emerged in China around 2008 and have since diversified into numerous novel reassortant viruses, including H5N2, H5N3, H5N5, H5N6 and H5N8. These novel viruses have since spread around the world, causing poultry outbreaks of H5N2 and H5N3 in Taiwan; H5N8 in South Korea, China, Japan and Europe; and H5N2 in USA and Canada[29]. Of particular concern is the H5N6 virus which has spread through numerous countries in Eurasia, and caused 36 laboratory-confirmed human cases resulting in 21 deaths[30]. H5N8 viruses have also been associated with seven asymptomatic human infections during a poultry outbreak in Russia[30]. Reassortment of H5N1 strains with other AIVs of public health concern such as H9N2, have also been reported, prompting concerns for the emergence of other novel lineages[31,32].

Despite the current low number of human cases, influenza H5N1 circulation in poultry has continued unabated. Viral surveillance in LBMs has established that H5N1 circulation is occurring at levels similar to those detected during the peak period of human infections[8–12]. The current lack of human H5N1 cases may be linked to the dominant strain currently circulating (clade 2.3.2.1) being more 'avian-like' and not as readily able to jump the species gap to infect humans[25]. However, in some countries, H5N6 reassortant viruses have replaced H5N1 as the dominant virus in circulation, thus highlighting the threat for the emergence of novel AIV viruses[33].

Conclusions

For the past ~25 years, AIV H5N1 has been regarded as one of the most pertinent threats for pandemic emergence. Fortunately, spill-over of the virus into humans has remained relatively low and the ability to transmit efficiently between humans has not been established. However, the widespread, intense circulation of H5N1 and H5Nx viruses across many regions of the world is an ongoing animal health challenge and a potential threat for public health. The propensity for these viruses to reassort with LPAIVs, particularly in the LBM environment, is a constant source for the introduction of

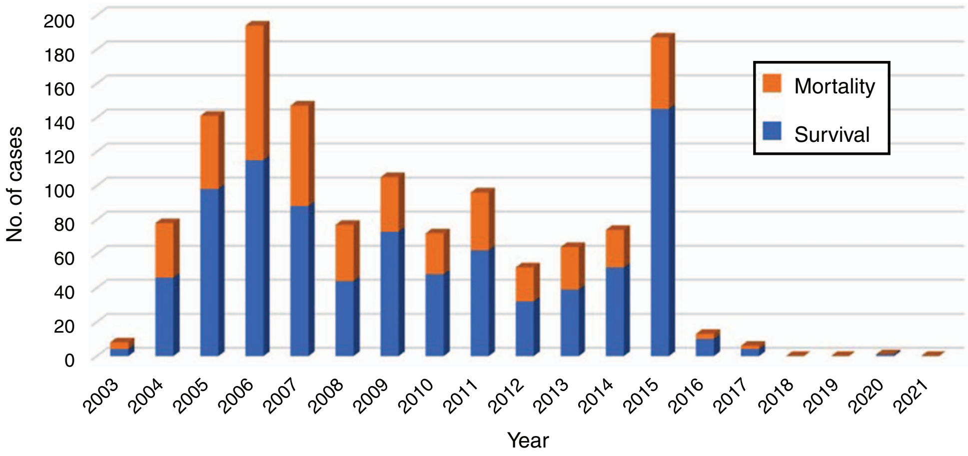

Figure 3. Global human cases of avian influenza H5N1 (2003–2021). Information was collated from: ProMed (https://promedmail.org/); and World Health Organization (https://www.who.int/publications/m/item/cumulative-number-of-confirmed-human-cases-for-avian-influenza-a(h5n1)-reported-to-who-2003-2021-15-april-2021).

novel viruses into poultry circulation. Surveillance of virus populations in LBMs is an important strategy of monitoring for the emergence of novel strains and may act as an early warning system to prevent major outbreaks of H5N1 (and other H5 viruses) in the human population.

Conflicts of interest

The author declares no conflicts of interest.

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Biography

A/Professor Paul Horwood is an Associate Professor of Virology and Viral Diseases at James Cook University. His research focuses on emerging pathogens and zoonotic diseases, with an emphasis on improving surveillance and laboratory diagnosis in resource-limited settings. He conducts research to better understand zoonotic transmission in high-risk interfaces where humans, domestic animals and wildlife interact.