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Animal and human influenzas

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Summary
Influenza type A viruses affect humans and other animals and cause significant morbidity, mortality and economic impact. Influenza A viruses are well adapted to cross species barriers and evade host immunity. Viruses that cause no clinical signs in wild aquatic birds may adapt in domestic poultry to become highly pathogenic avian influenza viruses which decimate poultry flocks. Viruses that cause asymptomatic infection in poultry (e.g. the recently emerged A/H7N9 virus) may cause severe zoonotic disease and pose a major pandemic threat. Pandemic influenza arises at unpredictable intervals from animal viruses and, in its global spread, outpaces current technologies for making vaccines against such novel viruses. Confronting the threat of influenza in humans and other animals is an excellent example of a task that requires a One Health approach. Changes in travel, trade in livestock and pets, changes in animal husbandry practices, wet markets and complex marketing chains all contribute to an increased risk of the emergence of novel influenza viruses with the ability to cross species barriers, leading to epizootics or pandemics. Coordinated surveillance at the animal–human interface for pandemic preparedness, risk assessment, risk reduction and prevention at source requires coordinated action among practitioners in human and animal health and the environmental sciences. Implementation of One Health in the field can be challenging because of divergent short-term objectives. Successful implementation requires effort, mutual trust, respect and understanding to ensure that long-term goals are achieved without adverse impacts on agricultural production and food security.

Keywords
Animal – Human – Influenza – One Health – Pandemic – Zoonosis.

Introduction

The concept of One Health has been aptly described as the 'collaborative efforts of multiple disciplines working locally, nationally and globally, to attain optimal health for people, animals and the environment' (1). Influenza in both humans and other animals causes significant morbidity, mortality and economic impact. Influenza type A viruses are found in birds and a range of other animal species, including humans, and have the capacity to undergo inter-species transmission, sometimes leading to epizootics and pandemics, and this provides an excellent example of the need for a One Health approach (2, 3, 4).

Influenza viruses

There are three types of influenza virus: types A, B and C. Influenza type A viruses infect a range of animal species, including humans. Influenza types B and C almost exclusively infect humans, although there are anecdotal reports of their being detected in other animals (5). This discussion is exclusively focused on influenza type A.

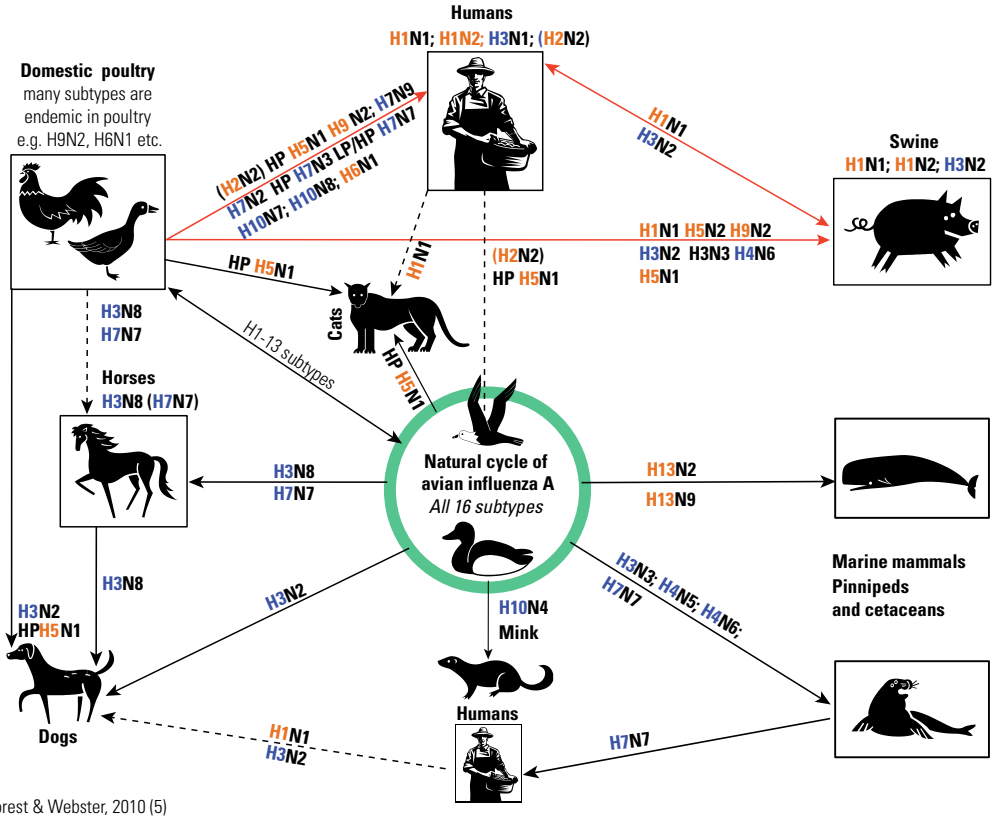
Influenza viruses are RNA viruses with a segmented genome; they are further subtyped on the basis of their viral surface proteins, the haemagglutinin (HA) and neuraminidase (NA). Until recently, HA subtypes 1–16 and NA subtypes 1–9 were recognised in aquatic wild bird reservoirs; only a few were established in mammalian species, including humans (5). More recently, H17 and H18, and N10 and N11, have been described in South and Central American bat species, suggesting that the diversity of influenza viruses is far from completely understood (6). The HA and NA subtypes can be found in different combinations, giving rise to a large diversity of virus subtypes, e.g. H1N1, H5N1, H7N9.

The lack of proof-reading in the influenza viral RNA polymerase leads to error-prone RNA replication and to

a high mutation rate in the course of virus replication. The segmented RNA genome allows the virus to undergo genetic reassortment when two different influenza viruses infect the same cell; thus, hybrid viruses containing gene segments of both parents may emerge (genetic reassortment). Recombination in the viral RNA genome is a third mechanism for the generation of genetic diversity. These mechanisms can act in concert, allowing influenza viruses to cross species barriers and evade host immune responses with great agility.

Influenza virus ecology and inter-species transmission

Aquatic wild birds (Anseriformes, Charadriiformes) carry a diversity of influenza A subtypes, H1–16 and N1–9, but H13 and H16 are largely restricted to species of gull within the Charadriiformes (reviewed in Forrest *et al.* [5]). However, only a few influenza subtypes have become established in mammals. Human epidemic or pandemic influenza has so far only been reported with subtypes H1, H2 and H3, although zoonotic infections have been reported with H7 (H7N7, H7N2, H7N3, H7N9), H5 (H5N1, H5N6), H9 (H9N2), H6 (H6N1) and H10 (H10N7, H10N8) (Fig. 1) (5). Only H1 and H3 have become established as lineages in swine, although other subtypes (H9N2, H5N1, H4N6) have been transiently isolated from this species. H3N8, and in the past H7N7, have become established in horses, sometimes having a major impact on the horse racing industry as well as on horses used in agriculture and transport. Equine H3N8 and avian H3N2 viruses have become endemic in dogs in North America and Korea, respectively (7, 8). Marine mammals (pinnipeds and cetaceans) have occasionally been reported to have acquired influenza viruses (H3, H4, H7, H13), presumably from aquatic birds.



Source: Adapted from Forest & Webster, 2010 (5)

Fig. 1

Overview of known influenza virus subtypes endemic in various species, and inter-species transmission events

Influenza subtypes H1–H16 and N1–N9 are endemic in wild aquatic waterfowl

Commonly endemic subtypes in each species are indicated below the species names. Subtypes within brackets are those that were endemic in these species in the past, but not currently. Solid black lines indicate inter-species transmission events which may or may not have led to long-term establishment of the subtype in the new species. The red solid lines indicate the most likely pathways by which a new influenza pandemic may arise. Parallel to each line are the subtypes reported to have been transmitted between those species. All virus subtypes denoted are low pathogenic (LP) unless denoted as HP, which indicates highly pathogenic avian influenza viruses. The 16 H subtypes are divided into two main groups and these are indicated as orange (group 1) and blue (group 2)

Although aquatic wild birds commonly carry diverse influenza A subtypes, only a restricted subset of these become established in domestic terrestrial poultry at any given place and time. It has been suggested that domestic ducks play a key role in the adaptation of influenza viruses from the wild aquatic avian gene pool to terrestrial poultry such as chickens. This was most recently seen in the emergence of H7N9 in terrestrial poultry (9) and has previously been described for H6N1 viruses (10).

Many avian influenza virus infections in terrestrial poultry (e.g. H9N2, H7N9) are largely asymptomatic or cause only mild clinical signs in terrestrial birds such as chickens or turkeys; they are designated low-pathogenicity avian influenza (LPAI) viruses. However, H5 and H7 subtypes can acquire multiple basic amino acids by mutations in the HA connecting peptide, which confers high pathogenicity in chickens and other terrestrial poultry. Such viruses disseminate beyond the respiratory and gastrointestinal tracts of the bird to affect other organs such as the brain, spleen and pancreas, leading to death (5).

Examples of viral genetic determinants that influence virus host range and inter-species transmission are summarised in Table I. Previously it was believed that both Siaα2-6 and Siaα2-3 glycans were abundant in the porcine respiratory tract and that both avian and human viruses could replicate in swine, giving rise to the hypothesis that pigs serve as a 'mixing vessel' for the emergence of pandemic influenza by being permissive for both human and avian viruses (11). More recently, it has become clear that swine are not so permissive to avian viruses. The Siaα2-3 in pigs appears to be restricted to the bronchioles rather than the upper airways (33). This perhaps explains why many avian viruses endemic in Asian poultry (e.g. H9N2, H5N1) have not become established in swine, even though these species often co-mingle and are co-housed in many parts of Asia. Even experimental infection of swine with avian H5N1 or H7N9 viruses did not lead to transmission from pig to pig (34, 35).

Overall, the molecular adaptations needed for an avian or swine influenza virus to adapt to efficient replication and transmission in humans are complex and multifactorial.

Table I
Examples of viral genetic factors that determine host restriction and inter-species transmission

Virus factors relevant in inter-species transmission	Mechanism of action	References
Haemagglutinin (HA) binding to host sialic acid (Sia) receptors	Aquatic avian species have Siaα2-3 linkages while the human upper airways have Siaα2-6 linkages, forming a species barrier. Glycosylation sites on the globular head of HA affect human adaptation. Glycan arrays now provide comprehensive profiles of binding Sia profiles of influenza, but these need to be interpreted in relation to glycans actually found on the human respiratory tract epithelium	11, 12, 13, 14, 15
Secondary sialic acid binding site with haemadsorbing activity in neuraminidase (NA)	Avian viruses have a secondary sialic acid binding site in NA which is lost in human viruses	16, 17, 18
Determinants affecting pH of HA activation	The optimal pH of HA activation differs for viruses from aquatic birds, terrestrial poultry, swine and humans	12, 13, 19
HA:NA balance	The HA binds to cell receptors while the NA cuts the virus free from the cell surface after virus replication is completed. These two activities need to be well balanced for optimal virus replication and inter-species transmission. Retaining such HA:NA balance following inter-species virus transmission from ducks to chickens is typically associated with deletions in the stalk of NA. HA:NA balance is also relevant when swine viruses adapt to human transmission (e.g. 2009 pandemic H1N1)	20, 21, 22, 23, 24
Polymerase proteins, e.g. PB2	The viral polymerase interacts with cellular proteins (e.g. importins) and also affects the range of optimal temperature for viral replication. The temperature of the human upper airways (33°C) differs from that of birds (42°C) and swine (38.8°C)	25, 26, 27
Molecular signatures in nucleoprotein (NP), matrix protein M1, non-structural protein NS1	Molecular signatures that differ in human and avian viruses	28, 29
NP	Myxovirus (MxA) susceptibility (not shown with transmissibility)	30
M1, M2 plus HA and NA	Enhance pdm09 transmission	31, 32

The need for a One Health approach to influenza

Pandemics emerge as a result of animal influenza viruses adapting to transmission in humans, either through reassortment with pre-existing seasonal human influenza viruses or through direct adaptation of animal viruses to humans (36). If such viruses have a variant HA or a novel HA subtype to which the human population has no prior immunity, the viruses will spread within weeks to affect many countries, as occurred with the 2009 H1N1 pandemic. Studies in Hong Kong showed that the novel pandemic H1N1 virus that was first recognised in Mexico in April 2009 had infected approximately 50% of children in Hong Kong by September 2009 (37). It was fortunate that the severity of the 2009 pandemic was lower than that of the previous pandemics in 1918, 1957 and 1968, because it had affected large numbers of people on many continents before any vaccine was available. Using current technologies, it takes at least six months from the identification of a pandemic virus for vaccine to be made available, and even longer to have adequate doses to immunise a significant proportion of the global population. This highlights the need for surveillance and risk assessment of animal viruses and zoonotic transmission events so that vaccine seed-stock development can be carried out pre-emptively, in advance of pandemic emergence.

Inter-species transmission among other animals can also lead to novel disease outbreaks. For example, from 1998 onwards, the emergence of the triple reassortant influenza A viruses with gene segments acquired from swine, human and avian viruses caused outbreaks in swine in the United States of America (USA) (38). Similarly, canine outbreaks of H3N8 virus in the USA in 2004 originated from equine influenza viruses (7).

The need for, and the challenge in implementing, the One Health approach is illustrated in the following case studies.

Case study: avian influenza H5N1

The emergence and spread of highly pathogenic avian influenza (HPAI) H5N1 in Asia provides a good illustration of the benefits and challenges in the application of the One Health approach (3, 4). The H5N1 lineage of HPAI that is currently endemic in some countries in Asia and in Egypt was first detected in Hong Kong in 1997. Following the depopulation of poultry that led to the apparent eradication of the virus from Hong Kong in 1997, active virological surveillance of apparently healthy poultry in live poultry markets in Hong Kong from 1999 to 2003 revealed that the virus continued to circulate in the wider region, undergoing genetic reassortment and changing its host range (3). Close collaboration between the government departments of animal and human health, together with academic researchers, led to the progressive implementation of evidence-based measures to contain this threat. These included enhancing biosecurity on farms and within markets, instituting changes in marketing practices in live poultry markets, including the implementation of 'rest days', and later the banning of live poultry being kept overnight within retail poultry markets. Control measures also included vaccination of poultry, aimed at preventing re-introduction after stamping out rather than as a means to suppress endemic virus circulation. This was indeed One Health in action, prior to the phrase becoming fashionable.

Other countries in the region did not respond effectively to the warnings that this virus was circulating in the wider region. When HPAI H5N1 was finally recognised and reported in nine other Asian countries or territories (South Korea, Thailand, Vietnam, Japan, Cambodia, Laos, Indonesia, mainland China, Malaysia) between December 2003 and August 2004, the virus had already become widespread and entrenched in many of them, making control extremely difficult. Those countries that did recognise H5N1 introduction early (South Korea, Japan, Malaysia) were able to stamp out transmission effectively. Of the others, only Thailand has been able to free itself from endemic H5N1 infection in its domestic poultry. A One Health approach was tried in Indonesia with the establishment of the National Committee for Avian Influenza Control and Pandemic Influenza Preparedness (KOMNAS FBPI) in 2006; this was a high-level multi-disciplinary committee that provided effective communication with senior levels of government. The lack of success in controlling the H5N1 threat in Indonesia was probably attributable to the widespread endemicity that had been established by the time the threat was recognised and, among other things, the decentralised nature of government control (reviewed in Daniels *et al.* [39]). From December 2003 to February 2006, the economic cost of HPAI H5N1 in East Asia alone was estimated to be US$10 billion (40). By 24 January 2014, HPAI H5N1 had led to 650 confirmed human cases, with 386 deaths, and this virus remains a significant pandemic threat. One may speculate how much of this tragedy for both animal and human health may have been averted by a more proactive surveillance strategy in the Asian region following the repeated warnings emanating from the One Health strategy implemented in Hong Kong.

The common features of those countries where HPAI H5N1 has become endemic include:

– complex and unmanaged poultry production and marketing chains, including widespread involvement of live poultry markets and backyard poultry

– relatively weak public and private veterinary services

– lack of a determined societal response to deal with the threat (41).

Human infection following exposure to HPAI H5N1 is so rare that the connection between poultry HPAI and human disease is not immediately apparent; therefore, the human health threat is poorly understood and not appreciated by the public.

It is of note that Thailand, the one country that succeeded in eliminating H5N1 infection from poultry after the virus had become endemic in domestic birds, had few live poultry markets and a determined centralised response to control, with public involvement in the surveillance and stamping-out programme without the use of vaccination, which was driven by the desire to restore the poultry export market (41, 42).

While migratory birds have contributed to the long-range spread of clade 2.2 (43) and clade 2.3.2.1 viruses, they are not the main reason for the endemicity of infection in most regions. Factors that make control of H5N1 so difficult in poultry include live poultry markets, transboundary spread associated with illegal movement of poultry, silent infection in ducks and the common practice of free-grazing duck husbandry and, in some countries, the role of fighting cocks. Inadequate or delayed reimbursement following the culling of affected flocks provides no incentive for prompt reporting and compromises efforts to control HPAI outbreaks (4).

Case study: avian influenza H7N9

April 2013 saw the emergence of a novel avian H7N9 influenza virus which now poses a zoonotic threat and is a cause of pandemic concern (44). The virus remains of low pathogenicity in poultry and infection of these species remains asymptomatic, making its control far more challenging than that of HPAI H5N1 virus. This virus was first detected as a novel virus in humans with severe pneumonia in the Yangtse Basin in Eastern China, and it then progressively spread to involve other provinces in Eastern and Southern China. On 28 February 2014, the number of human H7N9 cases stood at 375, with almost one-third of these being fatal (45). The cases occurred in an initial wave (n = 133) from February to May 2013, only two cases were reported in July and August, but since October 2013, a second wave of cases (n = 240) has emerged. The new wave of cases from October 2013 to February 2014 spanned a wide geographical region, suggesting that the virus is now widely entrenched in China. Most human cases have been associated with exposure to live poultry or to wet markets in which live poultry are sold (45). An intervention that involved the closure of live poultry markets in the major cities of Shanghai, Hangzhou, Huzhow and Nanjing in April 2013 was associated with a rapid reduction of cases in these regions, confirming the role of poultry as the source of human infection (46). The outbreak and the measures taken to control it had a huge economic impact on the poultry industry in affected areas.

The reduction of human cases in the summer of 2013 was followed by a resurgence of cases in the cooler winter months. Circulation of avian influenza viruses is known to increase in the cooler months of the year (22, 47). The H7N9 virus is unusually adapted to the human respiratory tract (48), and possesses some capacity for airborne transmission in ferrets (35), highlighting its significant pandemic potential. In contrast, the number of poultry premises on which the virus has been detected is currently much lower; in 2013, only 23 premises in China sent reports of virus detection to the World Organisation for Animal Health (OIE). In most of these cases, the virus was detected as part of the epidemiological follow-up of human cases (OIE World Animal Health Information Database, www.oie.int). Thus, disease in humans largely acts as a sentinel for infection in poultry. This illustrates the One Health dilemma. Surveillance for this virus in poultry provides no benefit to the poultry industry; on the contrary, finding evidence of H7N9 would have major negative economic consequences. However, it is crucially important to monitor, and if possible contain, this zoonotic and potentially pandemic threat.

Other avian influenza viruses of relevance to One Health

Subtype H9N2 is widely endemic in poultry across Asia and the Middle East and has repeatedly been detected in humans with relatively mild influenza-like illness. An outbreak of HPAI H7N7 in poultry in the Netherlands led to almost 100 human infections, largely involving conjunctivitis or influenza-like illness but one fatal infection with severe viral pneumonia occurred. This outbreak was contained by culling affected poultry flocks. There have been other zoonotic transmission events involving H7 subtype viruses, but the source of these outbreaks has been rapidly eradicated (49). Recently, an H10N8 virus was detected in a person with underlying disease in China (50), and infection with an H6N1 virus was reported in Chinese Taipei (51). However, isolated zoonotic events involving novel viruses, though noteworthy, are unlikely to pose major human health risks.

Case study: swine influenza

Influenza viruses endemic in swine and humans apparently have a similarly restricted range of subtypes: H1 and H3 are endemic in both species (52). In contrast to avian influenza viruses, there is two-way traffic of influenza viruses between humans and swine. The H1N1 influenza viruses that emerged in 1918 caused a pandemic in humans and an epizootic in swine. It is generally believed that this virus spread from humans to swine, although the reverse route of transmission cannot be ruled out. After persisting in swine for 81 years, by which time the swine and human H1 haemagglutinins had markedly diverged antigenically, the same H1 lineage re-emerged, after reassortment, to give rise to the 2009 H1N1 pandemic (53).

As this 2009 pandemic H1N1 virus spread worldwide, it was transmitted back to swine in many parts of the world, and it has dramatically changed the global landscape of swine influenza viruses. After reverse zoonosis of the pandemic 2009 H1N1 virus to swine, it reassorted with locally endemic swine influenza viruses to give novel reassortants with one or more 2009 H1N1 pandemic virus gene segments (54, 55). In China, these reassortants with pandemic H1N1 gene segments have currently become the most prevalent swine influenza viruses in circulation (56), but their impact on animal and public health remains unclear (56). An H3N2 swine influenza reassortant carrying the pandemic H1N1 matrix (M) gene segment has infected many humans in the USA, causing >300 cases and one death in 2012 (57). Many of these infections have occurred in children exposed to swine at agricultural fairs where humans and livestock come into close contact. Interestingly, in areas where there were no endemic swine influenza viruses to permit further reassortment, the 2009 pandemic H1N1 viruses repeatedly spilling over from humans to swine failed to establish a permanent lineage within swine (58).

While other avian influenza virus subtypes have been transiently detected in swine (e.g. H9N2, H5N1, H4) none of them has given rise to established lineages in swine (52, 56). The limited range of subtypes that have become endemic in humans (H1, H2, H3) and in swine (H1, H3) raises the question of whether these subtypes, and not others, have a particular predilection to adapt to transmission in these two species.

With the ongoing global perturbation of swine influenza virus genomics following the influenza pandemic, and because swine influenza is largely asymptomatic in swine, it is even more urgent that virological surveillance for influenza is enhanced (52). Given the limited benefit of such surveillance for the swine industry, there is no incentive for the industry to participate in such surveillance unless measures are taken to avoid negative outcomes arising from any positive surveillance results. Surveillance in abattoirs (anonymised if necessary) has been successfully employed as one means to minimise the negative impact on individual producers (54).

One Health strategies to contain risks to human and animal health

Surveillance for pre-pandemic vaccine development

The pandemic threat posed by animal influenza and the speed with which such pandemics spread highlight the need to get 'ahead of the curve', without compromising the economics of animal husbandry. This necessitates good surveillance in humans to detect novel zoonotic transmission events, surveillance in animals to identify viruses of potential pandemic concern and risk assessment of such information to provide guidance for pre-emptive action, which may include: stamping out potential viral threats in animals; initiating the development of vaccine seed strains and the reagents for potency testing; and, if warranted, making seed-lots of virus or stockpiling pre-pandemic vaccines. The World Health Organization (WHO) influenza vaccine strain selection meetings, held twice yearly, consider potential pandemic threats from animal viruses and make recommendations on strains for use in pre-pandemic vaccines against viruses such as H5N1, H9N2 and H7N9, and variant swine influenza H3N2 (59). This is based on ongoing surveillance and the genetic and antigenic characterisation of relevant field isolates from human zoonotic infections, as well as from animals. Many of these activities require coordination and collaboration among the animal health, human health and environmental sectors and require the One Health approach (see below).

Surveillance of influenza A viruses in animals for pandemic preparedness poses a number of major logistical challenges, some of which have been highlighted in the case studies above. Influenza A viruses are found in a range of wild and domestic animal species, and many pose little or no threat to humans or other species. Surveillance of influenza A viruses in animals is understandably focused on viruses that cause significant disease outbreaks in domestic livestock. Highly pathogenic avian influenza viruses in poultry typically arise from influenza A subtypes H5 and H7. However, the pandemics of the past 100 years (i.e. the ones we know about) arose from influenza A subtypes H1, H2 and H3, which were very likely to be of low pathogenicity in poultry or swine. Influenza in swine typically causes few clinical signs.

Influenza virus infection in wild aquatic birds is largely asymptomatic, but there is some evidence of a subtle fitness cost to the bird in terms of migrating capacity and range (60). Overall, however, other than the desire to protect wild birds from misinformed culling efforts, there is little incentive for the environmental sector to carry out surveillance of influenza viruses in wild birds. Thus, carrying out influenza virus surveillance in domestic or wild animals to monitor pandemic risk is of little benefit to the environmental or animal health sectors; it is an activity that is largely driven by the desire to reduce the risks (however remote) to humans. Moreover, the environmental and animal health sectors do not usually receive funding to carry out such work. On the contrary, there is a disincentive to carry out work to find influenza viruses in domestic livestock in the absence of overt disease because it can cause needless concern among consumers or adversely affect export markets and have a significant negative economic impact.

Risk assessment

Only rarely do animal viruses pose any threat to other animal species, including humans. Assessing the risk associated with the findings of influenza surveillance in animals is therefore of the utmost importance. The viral genetic determinants that confer transmissibility in humans are poorly understood (see Table I). Transmission by the airborne route among ferrets is accepted to be the best surrogate for the transmissibility of influenza viruses in humans (12, 61). The binding of virus to glycan arrays with a range of sialic acids can help identify avian viruses with a predilection for binding to human receptors of type Siaα2-6. The tropism of viruses for *ex vivo* cultures of human tracheobronchial epithelium gives a more direct assessment of the adaptation of an animal virus to the human respiratory tract (48, 62). Detecting a lack of cross-reactive immunity in the human population would be an important part of pandemic risk assessment. Algorithms for such risk assessment of animal viruses for pandemic threat have been developed and continue to be refined (63). Better understanding of the viral molecular determinants associated with human-to-human transmission of avian or swine viruses remains an important aspect of ongoing research (64). Some understanding has been achieved with avian H9N2 and H5N1 and swine influenza viruses, but more research is needed in this area (12, 13, 23, 31, 61).

Prevention at source

The concept of prevention at source aims to shift the paradigm from detection, assessment and response once an outbreak has occurred to interventions that may avoid such emergences in the first place (65). If the ecological and epidemiological determinants underlying the emergence of zoonotic infections, pandemics or epizootics can be understood through case studies of such events, interventions can be implemented that would reduce the risk of the emergence of such threats. Such research, as well as policy implementation, requires the One Health approach (3, 4).

Reducing exposure

In Asia, zoonotic infections with avian influenza viruses, whether they be H5N1, H7N9 or another type of influenza virus, are largely acquired through exposure at wet markets selling live poultry, exposure to sick poultry or bathing in waters potentially contaminated with virus (45, 66, 67). The closure of live poultry markets (LPMs) is an effective intervention to reduce human exposure and infection (46). Wholesale and live poultry markets are such a potent source for virus infection because they serve to amplify, maintain and disseminate avian influenza viruses. Evidence for this comes from many independent sources. Rest days, on which the LPM is emptied, followed by restocking the next day, reliably lead to a reduction of avian influenza viral isolation rates (68). Banning the keeping of live poultry overnight within the market reduces viral isolation rates even more dramatically (47). The surfaces within these markets, and especially the surfaces and tools used in the slaughter of poultry, tend to be highly contaminated with influenza viruses, such as HPAI H5N1, in endemic areas (69). Thus, even if LPM trade is not completely banned, interventions such as rest days, together with the cleaning of these premises and/or banning the holding of live poultry overnight in LPMs, can significantly reduce the risk of human exposure and infection. The reservoir and amplifier effects within the LPM also contribute to the dissemination of the virus back to farms via poultry cages, fomites and personnel. In a case-control study of H5N1-infected farms in an outbreak in Hong Kong in 2002 it was found that farms selling poultry directly to the LPM (rather than via the wholesale market, where cages are washed and changed) was a major risk factor for infection of the farm (70). Thus, while the LPM is a 'dead end' for the poultry, it is not a 'dead end' for the virus. These mechanisms are likely to be the main drivers for the spread of the current H7N9 outbreak in China. Similar findings on the role of LPMs in amplifying and disseminating influenza viruses have been reported in the USA (71, 72). Thus, relatively simple interventions at critical points in the poultry supply chain may dramatically reduce human health risks from avian influenza (73).

The greatest risk factor for human infection with the variant H3N2 swine influenza virus in the USA was exposure to swine at agricultural fairs (74). It is very likely that amplification of occasionally introduced virus occurs in this setting in a similar way to that described for LPMs.

Reducing emergence of novel influenza viruses

Some aspects of the upstream determinants of influenza disease emergence are understood. HPAI influenza generally arises from LPAI subtypes H5 and H7. Thus, the emergence of LPAI viruses of these two subtypes in poultry is recognised as a trigger for aggressive pre-emptive intervention and is reportable to the OIE. Such introductions to domestic poultry typically arise from wild birds and, therefore, it makes sense to avoid siting industrial poultry production near areas frequented by migrating wild birds. Viral genetic studies on the emergence of currently endemic H6N1 and the recently emerged H7N9 viruses in poultry demonstrate that these viruses have gene segments from wild birds as well as from domestic poultry (chickens, ducks), and that domestic duck populations probably provide the interface for such reassortants to emerge (9, 10). Segregating domestic ducks from chickens at all stages of the production and marketing chains may reduce opportunities for the emergence of such novel viruses, and this was one of the interventions introduced in Hong Kong in the aftermath of the HPAI H5N1 outbreak in 1997 (3).

While the separation of ducks and chickens at the backyard level is not achievable in practice, this may not be as critical as it appears. It is the large-scale industrial producers, and the complex wholesale and retail marketing systems they supply, that are more likely to facilitate such rare stochastic events and amplify, perpetuate and disseminate any novel viruses that emerge (75). In current poultry production systems in China, large industrial farms supply wholesale markets in large cities where there is co-mingling of ducks, chickens, quail, pheasants, chukar and other poultry species, providing the ideal milieu for virus emergence (Fig. 2). As was mentioned above, viruses generated in such wholesale or retail poultry markets can readily find their way back to the farms through cages, fomites and personnel. A parallel with the emergence of severe acute respiratory syndrome (SARS) is that, while the consumption of wild game meat in the winter months is traditional and has been practised for centuries, it was the large-scale game animal markets that arose from the increasing affluence of Guangdong Province that provided the scale of animal co-mingling that permitted the emergence of SARS in the 21st Century (65).

One Health initiatives

In recent years, a number of initiatives have been introduced to coordinate and synergise activities between the human and animal health disciplines, to optimise outcomes. The tripartite agreement among WHO, the OIE and the Food and Agriculture Organization of the United Nations (FAO) aims to share responsibilities and coordinate global activities to address health risks at the animal–human–ecosystems interfaces. Key operational elements include joint cross-sectoral coordination mechanisms, communication, joint simulation exercises, data-sharing, joint risk assessment and active cooperation on disease control programmes (76). Influenza is one of the three priority areas selected for the initial operation of this collaboration. In some regions in Africa and Asia, joint field epidemiology training courses (for physicians, laboratory scientists, and epidemiologists working in human and animal health) are under way to allow joint investigation of zoonotic infections (77, 78). Some of these are not exclusively focused on influenza: the training and practice target zoonotic infections that are locally relevant and focus on issues associated with the animal–human interface in the local area. A four-way linking project that links veterinary epidemiology and laboratory information with human health epidemiology and laboratory information is currently being implemented to assess health risks at the animal–human interface in selected H5N1 endemic areas (e.g. Egypt, Vietnam, Indonesia, Bangladesh) (79).

The OFFLU network is an OIE and FAO consortium that 'aims to provide early recognition and characterisation of emerging influenza viral strains in animal populations, and effective management of known infections, thereby better managing the risk to human health and supporting global food security, animal health and welfare, and other community benefits derived from domestic animals and wildlife'. Representatives of OFFLU participate in the bi-annual WHO influenza vaccine strain selection meetings, providing input on field data and the antigenic and genetic characterisation of relevant animal influenza viruses, such as HPAI H5N1, H9N2 and H7N9, for vaccine development.

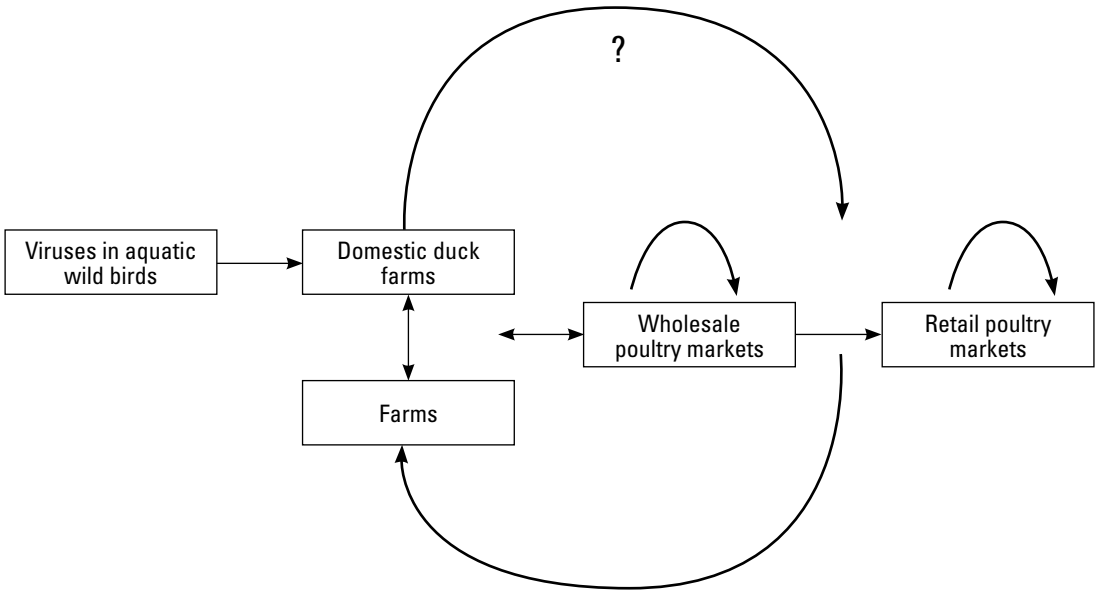


Fig. 2
Probable routes of virus transmission through the poultry marketing chain
Adapted from Sims & Peiris, 2013 (3)

Other examples of One Health or 'Eco-Health' initiatives include the following. In Cambodia, a project called 'Healthy Livestock, Healthy Village, Better Life' closely involves village health workers as well as village animal health workers, with the aim of improving reporting of deaths in poultry and reducing poultry mortality. The villagers are taught how to implement simple quarantine measures in their village/household if any household has an increase in sick and dead poultry (77). In Asia, the Asia Partnership on Emerging Infectious Diseases Research (a research network composed of researchers, practitioners and senior government officials from Cambodia, China, Laos, Indonesia, Thailand and Vietnam) aims to improve control measures and policy across the animal–human–environment interface (80).

Conclusion

One Health approaches to the control of influenza are clearly desirable and have been practised in a few settings for many decades. They are necessary in the response to outbreaks as well as for devising pre-emptive policies for 'prevention at source'. Implementing such strategies in the field can be challenging because of divergent short-term objectives. Short-term pain may be the price to pay for long-term gain, and the meaningful implementation of One Health requires trust, understanding and effort to ensure that desirable outcomes are achieved without adverse impacts on agricultural production and food security. Compromising the food chain can lead to morbidity and deaths just as effectively as influenza can. Including the One Health concept in both undergraduate and graduate courses of human and veterinary medicine (and in integrated cross-disciplinary postgraduate training of human and veterinary epidemiologists, clinicians and laboratory scientists) will facilitate joint investigation of zoonotic infections and will help to put into operation the One Health agenda.

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Les grippes animale et humaine

M. Peiris & H.-L. Yen

Résumé

Les virus influenza de type A, qui affectent l'homme tout comme les animaux sont responsables d'une morbidité et d'une mortalité importantes et ont un impact économique considérable. Les virus influenza de type A sont dotés d'une capacité d'adaptation qui leur permet de franchir les barrières d'espèce et d'esquiver les défenses immunitaires de l'hôte. Certains virus dont la présence n'entraîne aucun signe clinique dans l'avifaune aquatique vont subir une mutation après avoir infecté des volailles domestiques, devenant ainsi des virus hautement pathogènes de l'influenza aviaire, capables de décimer des élevages entiers de volailles. D'autres virus responsables d'une infection asymptomatique chez les volailles (par exemple le virus A/H7N9 d'apparition récente) peuvent en revanche occasionner une zoonose extrêmement grave et représentent une menace pandémique majeure. La grippe pandémique surgit à des intervalles irréguliers et imprévisibles à partir de virus d'origine animale ; la vitesse de sa propagation à l'échelle mondiale devance de loin les capacités techniques actuelles de fabrication de vaccins dirigés contre ces nouvelles souches virales. La menace que la grippe fait peser sur l'homme et sur les animaux constitue un excellent argument en faveur de la démarche « Une seule santé ». Les changements intervenus en matière de déplacements, d'échanges d'animaux d'élevage et d'animaux de compagnie, de pratiques d'élevage, de marchés de produits frais et de complexité des chaînes de distribution sont autant de facteurs d'aggravation du risque d'émergence de nouvelles souches virales de la grippe capables de franchir la barrière d'espèces et de déclencher une épizootie ou une pandémie.

L'exercice d'une surveillance concertée à l'interface animal–homme dans le cadre de la préparation à l'éventualité d'une pandémie et les activités d'évaluation du risque, d'atténuation du risque et de prévention à la source requièrent une collaboration entre les praticiens de la santé animale et humaine et les sciences de l'environnement. La mise en œuvre d'une stratégie « Une seule santé » sur le terrain est une tâche difficile en raison des divergences entre les objectifs à court terme poursuivis par les différents acteurs. Une mise en œuvre réussie exige des efforts, une confiance mutuelle, du respect et une compréhension réciproque, afin de s'assurer que les objectifs à long terme soient atteints sans entraîner d'effets indésirables sur la production agricole et la sécurité alimentaire.

Mots-clés
Animal – Homme – Influenza – Pandémie – Une seule santé – Zoonose.

Influenza animal y humana

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Resumen
Los virus de la influenza de tipo A, que afectan al ser humano y otros animales, son causa de una importante carga de morbilidad y mortalidad y tienen importantes repercusiones económicas. Estos virus presentan adaptaciones que les permiten salvar las barreras entre especies y eludir la inmunidad del anfitrión. Virus que no causan signos clínicos en aves acuáticas salvajes pueden adaptarse a las aves de corral domésticas y convertirse en virus de influenza aviar altamente patógena que diezman a las bandadas. Virus causantes de infección asintomática en las aves de corral (como el virus A/H7N9, de reciente aparición) pueden dar lugar a una grave enfermedad zoonótica y constituir una importante amenaza de pandemia. La influenza pandémica se origina a intervalos impredecibles a partir de virus animales, y en su propagación mundial supera la velocidad con la que hoy en día, con la tecnología existente, pueden fabricarse vacunas contra esos nuevos virus. La amenaza que supone la influenza para el ser humano y otros animales ejemplifica perfectamente por qué necesitamos los planteamientos de «Una sola salud». Los cambios experimentados por el comercio, la venta de ganado y mascotas, la evolución de las prácticas zootécnicas, los mercados de animales vivos y las complejas cadenas de comercialización son otros tantos factores que acrecientan el riesgo de que aparezcan nuevos virus gripales capaces de cruzar las barreras entre especies y dar lugar así a epizootias o pandemias. La vigilancia coordinada en la interfaz entre personas y animales con fines de preparación para pandemias, determinación y reducción de riesgos y prevención de la enfermedad en su origen exige una labor concertada entre los profesionales de la salud humana, la sanidad animal y las ciencias ambientales. A veces, debido a la existencia de objetivos a corto plazo divergentes entre todas esas instancias, resulta difícil aplicar sobre el terreno los planteamientos de «Una sola salud». Para tener éxito en la empresa se requiere no solo esfuerzo, sino también confianza, respeto y entendimiento mutuos para lograr que se cumplan los objetivos a largo plazo sin que ello repercuta negativamente en la producción agrícola o la seguridad alimentaria.

Palabras clave
Animal – Influenza – Pandemia – Ser humano – Una sola salud – Zoonosis.

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