

The role of animal reservoirs in social–environmental landscapes: remarks on the control of avian influenza and preparedness for pandemics

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Summary

Influenza viruses are well known for their ability to infect and cause disease in a broad range of hosts. Modern advances in reverse genetics have enabled scientists to probe the mutations that allow influenza viruses to perform host switching. Despite this detailed understanding of the molecular modifications that allow host switching and adaptation, there is a gap in knowledge regarding the factors external to the virus and their interactions that act as triggers leading to a pandemic. Studies on the ecology of zoonotic pathogens should be the new paradigm for understanding not only influenza viruses but any

other infectious disease that can be a threat to animal and human health. The literature regarding influenza pandemics and influenza virus reservoirs was reviewed to analyse how social and economic changes can influence the appearance of new outbreaks of influenza. In addition, the importance of new research in a dynamic environment driven by the expansion of human territories and animal production systems is highlighted. A new paradigm is proposed for novel research approaches to infectious diseases such as influenza.

Keywords

Disease ecology – Ecosystem remodelling – Influenza virus – Pandemic – Reservoir – Spill-over.

Introduction

Influenza viruses have a broad range of susceptible hosts, which has favoured spill-over from aquatic birds to other avian species and to mammals, including humans. The biological characteristics of influenza viruses give them the capability to mutate at very high rates, resulting in viruses that can infect and eventually establish themselves in new host populations. Both of these traits are exemplified by pandemic influenza virus strains that ultimately become adapted to humans, causing recurrent seasonal epidemics (1, 2, 3).

Examples of this include the strain of influenza virus that caused the Spanish influenza pandemic in 1918 (resulting in more than 20 million deaths) (4) and the most recent pandemic in 2009. In preceding years it had been observed that the frequency of outbreaks and pandemics had an interval of more than 11 years, and that there is a cyclic presentation of the subtypes causing major epidemics or pandemics in human populations. The factors that restrict host range, mechanisms of adaptation of influenza viruses to new hosts, and host–pathogen interactions that explain the appearance of new influenza viruses constitute a complex system that has become a priority for research on influenza viruses (5, 6, 7).

The main objective of this paper is to present a comprehensive review and analysis of the state of the art in relation to influenza virus evolution, describing the most significant influenza pandemics, and addressing the importance of ecosystem modifications and animal species in the dynamics of the disease. The most relevant facts regarding influenza virus and factors that might be considered when approaching the dynamics of the disease are discussed.

Features of the virus and relevant epidemiology, from the devastating 1918 Spanish flu through the 21st Century

Influenza viruses belong to the *Orthomyxoviridae* family and the genus influenza virus. The genome is composed of eight segments of single-stranded RNA, organised as ribonucleoprotein complexes. The virions are enveloped and have a diameter of 80–120 nm with a length of 200 nm. The virus is capable of generating new strains by undertaking genetic reassortment inside a cell that has been infected with more than two strains of influenza virus simultaneously (8, 9, 10).

The structural characteristics that allow the virus to interact with host cells include two spike-like molecules located at the cell surface of the virions. The haemagglutinin (HA) glycoprotein, a type I molecule, is rod shaped and allows the virion to enter the cell by attaching to the host cell's sialoligosaccharides. Once the HA has attached to sialic acid receptors, the virus will enter the cell by endocytosis. A low pH in the endosome is needed for the HA to be activated and to expose the fusion peptide so the virion envelope can fuse with the endosome membrane. In contrast, the neuraminidase (NA) glycoprotein type II molecule is mushroom shaped. It allows the release of virions from the cell and removes acquired sialic acid residues from the host cells and virions, preventing the aggregation of the progeny viruses (11, 12).

The ongoing story of ever-present influenza: how influenza viruses have adapted along with humans

Influenza viruses use different mechanisms to infect new susceptible hosts and cause a pandemic, for instance a new avian descendant virus (e.g. the H7N9 strain), or genetic reassortment of different genes which will allow spill-over and result in animal influenza viruses that can jump to humans without further reassortment (13, 14, 15, 16). Pandemics caused by influenza viruses have been documented since the 16th Century (17). Although there are no records of the death toll of an early pandemic that occurred in 1889, data show that it was caused by an H3N8 influenza virus strain. After this, the well-known devastating influenza pandemic referred to as the ‘Spanish flu pandemic’ occurred in 1918–1919 (18, 19, 20).

The 1918–1919 pandemic had three waves of occurrence across Europe, Asia and the United States, Mexico, Colombia, Brazil and Peru. Despite the great impact of the Spanish flu, little is known about the epidemiology of this pandemic (20). It is presumed that at least 50 million people died, in most cases from pneumonia resulting from a secondary bacterial infection. The symptoms were so unusual that it was first confused with dengue fever, cholera or typhoid (20, 21). The 1918 H1N1 strain is known to be an avian influenza virus (AIV) which did not undergo any reassortment with human influenza strains, but instead evolved to be able to infect human cells and adapted enough to be transmitted from person to person.

Thirty-nine years after the 1918 pandemic, in 1957, another influenza pandemic occurred. This pandemic, caused by an H2N2 strain, was less severe and caused fewer deaths than that associated with the H1N1 virus in 1918. This H2N2 virus acquired the HA (H2), the NA (N2) and the polymerase basic protein 1 (PB1) genes from an avian virus and the remaining genes were from a previously circulating virus. Another moderate pandemic, caused by an H3N2 virus, took place in 1968. This virus also arose due to genetic reassortment, in that the HA (H3) and the PB1 genes were from an AIV. Five genes from the H3N2 strain related to the 1918 strain are currently

circulating in the world. The virus responsible for the 1918 influenza pandemic is very important because the reservoir has not yet been identified and its eight genes differ from those of any virus analysed between 1917 and 2009. As mentioned previously, the 1918 virus strain gave rise to H3N2, which caused a pandemic of moderate impact and also left progeny that 41 years later caused a pandemic (H1N1 2009) which, by July 2010, had resulted in an estimated 18,449 deaths (19, 20).

The challenges for the 21st Century with regard to the appropriate surveillance of viruses such as influenza include the effective detection of animals and locations that can act as catalysts for the development of new influenza virus strains. It is believed that influenza pandemics can occur at intervals as long as 39 years and as short as 11 years, but new global trends have brought new climatic, social and economic patterns that should be assessed before making such statements (6, 17, 22, 23). From this perspective, agricultural expansion, globalisation, overpopulation and climate change have become risk factors for the development of new influenza viruses (24, 25).

With regard to AIVs and their role in influenza pandemics, before the H1N1 pandemic of 2009, a new strain of AIV became important for humans in 1997 when a highly pathogenic avian influenza H5N1 strain was reported in Hong Kong. At that time the virus spread rapidly throughout Asia, but it has not been able to cause a pandemic so far (26, 27, 28). It is known that H5N1 virus can be transmitted from person to person in some specific cases; it is also known that backyard poultry play a role in the maintenance of the virus, and that close contact of humans with birds, either in markets or in cock-fighting clubs, plays an important role in the transmission of the disease (29, 30). Since 1997, countries such as Indonesia, Vietnam, Egypt, China and Cambodia have reported human cases of H5N1 influenza. These cases usually occur in people that live in rural areas, and the disease affects both young and old individuals. Since 2003, 844 cases and 449 deaths (as of October 2015) have been reported by the World Health Organization (31, 32, 33, 34).

The H5N1 virus was limited to Asian and Middle Eastern countries until 2014, when a Canadian woman who had travelled to Beijing, China, was admitted to a hospital in Canada and found to be positive for H5N1 influenza virus. The patient was treated, but she died on 3 January 2014. Although poultry markets are considered to be one of the main risk factors for H5N1 AIV transmission, the interaction of migratory birds and human socio-economic behaviour needs further study (29, 30, 35, 36, 37).

In February 2013, while the H5N1 virus was still circulating in Asia, another influenza virus emerged. China reported a new strain that was causing pneumonia in humans: H7N9 AIV (29). The H7N9 virus is known to circulate in wild birds and ducks, but no human case had been reported before this event. Such AIV strains are of low pathogenicity in birds, which means that birds will not develop disease or die, making surveillance in these species difficult. As a result, humans will act as sentinels of the disease (35, 38, 39). However, H7 subtype viruses have been present in enzootic outbreaks in birds; in addition, their ability to undergo genetic mutation and become highly pathogenic in birds has been documented. Viruses of this subtype have also caused infection in other mammals, for instance H7N7 viruses that emerged in 1956 and the H3N8 that appeared in the 1960s co-circulated, infecting horses for decades, with the former H7N7 virus subtype being replaced by the H3N8 from 1979 (11, 20).

It is important to mention that the genome of the H7N9 strain of AIV that infected humans in 2013, and that is currently circulating in China, had its origin in three different avian sources, which gave the new strain the molecular characteristics that allow transmission from person to person (39, 40, 41). Although none of the viruses from which the H7N9 strain originated has caused a significant outbreak or pandemic, the basic characteristics and current situation of the three avian viruses, the H7N9, and the H7N3 and the H2N6 that gave rise to the H7N9 influenza virus strain, need to be addressed. The H7N3 strain has caused disease in humans and birds since 1994, it has been isolated from a wild duck (*Anas platyrhynchos*), poultry and domestic turkeys in Italy, and it was isolated from a wild bird in China in 2011.

Human cases have been reported from Mexico, Canada and the United Kingdom (12, 42, 43).

In addition, H9N2 strains are endemic in poultry from Asia to the Middle East and some countries of Europe and Africa. Seemingly, H9N2 influenza virus was first isolated from humans in Hong Kong in 1999, where a total of four cases were reported. Although not many cases have been reported, the last human case was in a seven-year-old boy in China in November 2013; this patient recovered, as have all the cases caused by H9N2 viruses (11, 41, 42).

Influenza viruses have been present throughout human history and it seems that they will continue to be. This is why the social, economic and environmental factors that may play a role in influenza outbreaks and pandemics should be understood, as well as the role of reservoirs, in order to be able to put in place adequate surveillance plans and preparedness for the next influenza pandemic (3, 43, 44, 45).

Ecosystem remodelling, reservoirs and human activity

The creation of new niches is increasing as a consequence of the rapid expansion of human populations, which are becoming established in territories that used to be entirely natural. Human populations have migrated from rural areas to cities; this expansion, which involves the introduction of roads, houses, etc. to new geographical ranges, increases contacts among humans, animals and infectious agents, creating opportunities for infections to jump the species barrier. Moreover, agricultural systems must meet the increasing demand by introducing more animals into production facilities, leading to habitat alteration, deforestation and increased close contact with wildlife (34, 46, 47).

Therefore, environmental, climatic and social factors contribute greatly to the emergence and maintenance of diseases. It has been postulated that the emergence of disease is an evolutionary response to new environments; this evolution includes new forms of a disease and microbial adaptation. Furthermore, host factors such as nutrition,

immunological status and access to health services also need to be understood and identified in order to correlate host, agent and environmental roles in disease emergence (1, 28, 46, 48).

It is clear that an understanding of geographical organisation, population size, proximity to wildlife and agricultural systems is necessary to assess the risk factors for disease. Both the emergence of new diseases and the changes, either molecular or epidemiological, in disease agents that enable them to become established in new populations must be considered. With regard to wildlife, it is necessary to point out the importance of the role of migratory birds and, recently, bats in influenza virus dynamics (49, 50, 51, 52).

Migratory birds are affected by climatic changes that alter migration patterns, affecting their flyways and favouring in some cases contact with domestic animals. This may alter the survival rate of pathogens outside the host, and it is in this context that reservoirs and susceptible animal species should be considered. The identification of the reservoirs of an agent such as influenza virus will contribute greatly to control of its transmission from wild to domestic animals (chickens and turkeys, for instance). Reservoirs play a role in maintaining the agent within a population and as a source for transmission. Consequently, there is a need to understand multi-host pathogens and population dynamics, as has been mentioned by different authors (22, 53, 54).

The role of animals in the dynamics of many diseases is clear, and should be evaluated, taking into account the human–animal–environment interactions and dependencies (46, 55, 56). This is particularly important for the pandemics mentioned above which included an animal reservoir in their appearance and transmission. The 2009 influenza pandemic caused by H1N1 has been associated with spill-over and reassortment of influenza viruses involving pigs. Traditionally, pigs have been identified as a species that acts as a ‘mixing vessel’ for influenza viruses, owing to the fact that they can be infected with human, avian and swine influenza viruses (57).

Recently, bats have also been identified as a reservoir for influenza viruses, along with coronavirus, filovirus, lyssavirus and others. In addition, their population arrangement, density, global abundance and diversity of species are features that make bats an ideal animal reservoir (58).

It was known that the H17N10 strain of influenza virus was circulating in bats from Guatemala and, in 2010, Tong and colleagues investigated whether similar influenza viruses were present in bats in South America (59). They sampled bats in the Amazon rainforest of Peru and found another influenza strain circulating: H18N11. The researchers concluded that sialic acid is probably not the only receptor for this virus and does not act as the substrate for virus release. The HA molecule does not contain the cavity necessary for linking with sialylated glycans; in addition, the molecule is negatively charged, which may cause a conflict between charges during receptor binding. One theory is that perhaps H17 and H18 do bind to sialic acid but the binding affinity is too weak to be detected; alternatively, the virus may have another protein-based receptor, as some paramyxoviruses do. Nevertheless, focus should be applied to the relationship between the viruses and the environment surrounding these reservoirs, which results in modifications in host–virus interactions (53, 58, 59).

Regarding the origin of H18N11, phylogenetic analyses have shown that this strain is most closely related to the H17N10 virus circulating in Guatemala, but is in a different lineage. Inevitably many questions remain related to these findings, and it is of great importance to conduct more investigations to better understand the molecular host–virus interactions of H17N10 and H18N11 in bats and in other species, as well as the role of bats in influenza virus spread and maintenance (53, 59). Close attention should be paid to poultry husbandry systems that may allow birds to be at risk of being in contact with bats. In addition, it will be of great use to understand bat social networks, in order to be able to map any alteration in the population that might be important in the appearance of a new influenza outbreak. The capability of H17N10 and H18N11 to

exchange genetic material with other influenza viruses remains unclear (58).

As mentioned previously, bats are distributed worldwide and can adapt very well to human environments, adopting buildings, bridges, tombs and mines as breeding, feeding or resting sites. Furthermore, they can travel for some 2,000 km, contributing to virus dispersal and infection of other animal species along their journey. They live in high density populations which contribute to the maintenance and exchange of viruses. Furthermore, they can be infected with many viruses and carry them asymptotically. Finally, risk factors associated with close contact with bat faeces and urine, as well as consumption of bat meat, are subjects for research (22, 24).

Major issues and challenges related to influenza viruses

Previously unknown infectious diseases affecting humans have appeared during the last decade at an alarming rate of almost two new diseases every year. Many have emerged from animal reservoirs and their products: some examples are human immunodeficiency virus (HIV), Ebola virus, West Nile virus, Nipah virus, hantavirus and new strains of AIV. For instance, more than three-quarters of infectious diseases that have affected humankind during the 20th and 21st centuries (emerging or re-emerging) have arisen from contact between humans and the animals that are reservoirs of these agents (27, 46, 48).

The emergence of zoonotic diseases is determined by different socio-economic and environmental factors. Despite the evidence supporting this, there remains a strong need to understand the environmental modifications that contribute to the emergence of new diseases, including a broader analysis of the reservoirs, their ecology, habits, and the interactions with their environment and with humans (1, 22, 33, 47, 48, 53).

The reality is that pathogens have found better opportunities for jumping the species barrier, and efforts should be focused on the

environments in which animal reservoirs, pathogens and humans interact (26, 53). The role of bats in influenza virus transmission and the potential of the virus to be transmitted from bats to animals that can allow reassortment, such as pigs or ducks, is still unknown (51, 58). Nevertheless, it is clear that human activities and habits can act as a trigger to allow the close contact of domestic and wild animal species, increasing the risk of outbreaks and spill-over (8, 18, 43, 44, 46, 53, 58, 59).

Influenza viruses have been present throughout history and different strains have emerged, some of which continue to circulate while others no longer remain but have passed their genetic material to other strains of public health importance. It is clear that AIVs have great economic and health impacts on humans and the livestock industry. It is for this and the other reasons given throughout this article that the role of existing and new reservoirs of the disease, as well as the environmental factors contributing to the emergence and maintenance of influenza virus, should be a priority for surveillance and control plans, not only in birds but in mammals and particularly in humans. By identifying the reservoir and the social and environmental factors that are involved during and after a pandemic, a thorough understanding of the pandemic risk may be achieved. Analysing the dynamics of the disease using the 'One Health' concept enables the environmental, animal and human health factors to be approached as one interrelated subject.

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