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Animal influenza epidemiology

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Abstract

Influenza A viruses exist within their natural host, aquatic birds, in a number of antigenic subtypes. Only a few of these subtypes have successfully crossed into other avian and mammalian hosts. This brief review will focus on just three examples of viruses that have successfully passed between species; avian H5N1 and H9N2 viruses and H3N2 viruses which have transmitted from aquatic birds to humans and then to swine. Although there are a number of other subtypes that have also transmitted successfully between species, these three selected examples have spread and evolved in different ways, exemplifying the complexity of influenza A virus epidemiology.

The virus

Influenza A viruses, members of the *Orthomyxoviridae* family, can infect a variety of animals although their natural hosts are aquatic birds [1]. Although the host range barriers are generally strong, a hallmark of influenza A virus epidemiology is the transmission of the virus between species. These interspecies transmissions generally result in a transient infection characterized by limited spread, whereas, on occasion, a stable lineage is established in the new host. The mechanisms that decide the fate of a virus in a new host are, however, poorly understood. Morbidity and mortality are rarely seen in the aquatic bird reservoir, and it is primarily when the virus enters another host that disease results.

Influenza A viruses are found in host populations across the globe with viruses often transmitting across large geographic distances. A combination of the following transmission mechanism may be a likely explanation for the spread of influenza strains: trade of live animals, movement of animals within production systems, spread via feed, water, or equipment, wild birds' migrations, people movement, illegal importations of animals or animal products, and animal competitive events (cocks fights, horses-races, etc). Perhaps not too surprisingly, in many cases the epidemiology of the virus is closely linked to the epidemiology of the host.

In birds, and mostly for reasons of commerce, strains are classified as either low or highly pathogenic avian influenza (LPAI and HPAI respectively) viruses. H5 and H7 subtypes may be HPAI while all the 16 known hemagglutinin subtypes (H1 to H16) may be LPAI. The difference in morbidity and mortality between LPAI and HPAI viruses may be extreme (from absence of symptoms to 100% mortality). Irrespective of the virus pathogenicity, very different clinical signs have been associated with influenza viruses depending on the strain and the host. Respiratory and/or intestinal tracts are the main targets for replication of influenza viruses but the tissue distribution may be much wider especially with HPAI strains.

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Changes in agricultural practices, enhanced animal health surveillance, and/or viruses' evolution may have contributed to the apparent increase in animal influenza outbreaks reported in recent times; influenza is an increasing concern for veterinarians worldwide.

The epidemiology

To state that we understand the epidemiology of animal influenza is without question false. Much of the difficulty lies in the fact that the epidemiologies differ depending on what animal host and what virus is under investigation. Different hosts can exert different selection pressures (either naturally or as a result of husbandry practices) and as a consequence the spread and evolution of the virus can be dissimilar. To illustrate this fact we have chosen to briefly describe the epidemiology of examples of three virus subtypes in different animal reservoirs. These examples are by no means exhaustive or are they more important or necessarily different from other subtypes. Instead, these three examples each differ in their epidemiology's; highly pathogenic H5N1 viruses simmered in Southeast Asia before abruptly disseminating over a large geographic area over a period of a few years; two lineages of H9N2 viruses have spread more gradually to a more confined geographic region of predominately Asia and the Middle East; reassortant H3N2 viruses emerged in U.S. swine in the late 1990's, spread rapidly within North America, but have since, with one known exception, remained confined to this location (Table 1). In addition to virus spread, these three examples differ in their degree of, and mechanisms for generating, diversity.

H5N1

The current HPAI H5N1 viruses all have hemagglutinin (HA) genes that have evolved from a common ancestor, i.e., it was a single virus that transformed from the LPAI to the HPAI form. From this point, and although considerable reassortment has occurred, the virus has now undergone genetic drift into a number of genetically and antigenically different clades (http://www.who.int/csr/disease/avian_influenza/guidelines/nomenclature/en/). The epidemiology of the current HPAI H5N1 strains in animals reflects to some degree the host range of the virus. The virus has been detected and isolated from domestic poultry [2], wild aquatic birds [3], birds of prey [4], vultures [5], swine [6], felines [7–11], and rodents [12]).

The earliest known virus of this lineage was isolated from a goose in Guangdong province, China, in 1996 and for the best part of the next decade likely circulated in Southeast Asia [13]. Although a number of other Asian countries reported outbreaks of the virus in 2004, the virus dramatically expanded its geographic range when it exploded through Europe late in 2005 [14] and Africa in early 2006 [15;16]. Among the infected hosts, some, such as swans or cats, play an interesting role as sentinels of the disease; they seem to be dead end hosts and indicate that the virus circulates in an area. Other species seem to be influenza vectors, either healthy carriers such as various duck species, or symptomatic spreaders such as poultry. Although the exact mechanism of the spread of this virus is topic for debate, the fact that it is able to infect hosts that traverse large distances, either through migration or trade, means that the virus likewise has a large distribution.

In addition to aiding spread, growth in different hosts may also have aided in the genetic drift in the viral HA gene. Although there are a number of viral lineages seen in Asia, there are geographic pockets where only single lineages have established. One of these pockets is in Indonesia where clade 2.1 viruses dominate. Apart from earlier isolates from Southern China [17], these viruses do not appear to circulate elsewhere. Viruses in Europe, Middle East, and Africa, likewise, all belong to clade 2.2 due to the limited spread of viruses from Asia to these regions. The fact that no other viral lineage has entered Europe, Middle East, and Africa suggests that the westward transcontinental spread of H5N1 is rare and that unique factors may have been present in 2005.

H9N2

Similarly to the H5N1 viruses, H9N2 viruses have also spread across a number of different countries. While the focus has been on H5N1 influenza virus as the one at the top of our “hit list” with pandemic potential both in poultry and people, H9N2 must not be underestimated. The H9N2 virus preceded the H5N1 viruses by transferring from wild birds to domestic gallinaceous poultry in Asia. Virologic surveillance from 1975–1985 in live poultry markets in Hong Kong detected H9N2 viruses only in apparently healthy domestic ducks [18]. However by the mid 1990’s H9N2 viruses had reached panzootic proportions across Asia, mainly in chickens but with infection in turkeys, pheasants, ostriches and domestic ducks [19]. Disease severity varied from mild respiratory signs to death depending on co-infecting organisms; vaccines have been developed and used in commercial poultry in several countries [19]. When virologic surveillance was resumed in Hong Kong in 1997 H9N2 viruses were found to be endemic in apparently healthy chickens, quail and domestic ducks. Two lineages of H9N2 viruses were identified in terrestrial poultry; one lineage was found predominantly in quail (A/Quail/Hong Kong/G1/1997 H9N2) [G1 lineage] and the other was found in many species represented by A/Duck/Hong Kong/Y280/1997 (H9N2) [Y280 lineage] [20]. Both of these lineages have continued to circulate in domestic poultry in Eurasia with the development of multiple reassortant genotypes [21] and the virus is also commonly isolated throughout the Middle East. Although H9N2 viruses have not been subject to the same intense scrutiny afforded to H5N1 viruses, it seems that their diversity is more limited than that seen in the A/Goose/Guangdong1/96 H5 lineage. The exact reasons for this are not apparent, although the H9N2 virus host range is substantially more restricted than that of the H5N1 viruses. Nevertheless, H9N2 viruses have shown tropism for humans, many have mammalian virus-like receptor preference, and they therefore constitute a substantial pandemic risk.

H3N2

Swine represent another major host reservoir for influenza viruses. Unlike avian hosts, they are, however, host to a much more limited range of viruses; these viruses being predominately of the H1N1 and H3N2 subtypes. Despite the presence of human-like H3N2 viruses in swine populations in other parts of the world, in the U.S. isolation of these viruses from swine was rare. Indeed, the classical H1N1 virus lineage was considered the sole influenza A virus in swine in this country. This situation changed in the late 1990’s when multiple H3N2 isolates were made from geographically disperse swine operations [22;23]. The viruses responsible for these outbreaks, with the exception of one, were reassortant viruses containing human virus (HA, NA, PB1), swine virus (M, NS, NP), and avian virus (PA, PB2) gene segments. The human and avian virus genes were novel components of these swine pathogens. By 1999 there was serologic evidence that the viruses had spread throughout the U.S. swine population, suggesting these viruses had started spreading well before first identified. Although a degree of antigenic drift has been seen in these viruses, genetic and antigenic diversity has been amplified by continued reassortment with sequentially appearing human H3N2 drift variants [24]. In these reassortment events the swine viruses acquired the HA and in some instance NA from the contemporary human strains. Within a short period of time, multiple lineages of H3N2 viruses entered the population. The challenge is to determine what factors aided this diversification of swine viruses. Although not all of the novel reassortants have been maintained, H3N2 viruses continue to circulate and at least two genetically defined groups remain [25]. In addition to their spread throughout the North American swine population, these H3N2 viruses have also transmitted from swine to turkeys causing headaches for this industry [26;27]. These viruses have also caused sporadic human infection [28;29]. Consistent with swine being their primary host, intercontinental spread of these viruses has appeared to be minimal with the only report of these viruses outside of North America being in Korea [30]; the transmission presumably through transport of animals or animal material.

Perspectives

The epidemiology of influenza is complex. This complexity is driven by a number of factors including the number of possible hosts and the intrinsic capacity of the virus for genetic and antigenic change. Although we understand some of the factors driving these properties of the virus, a number remain undefined. Some of the areas that need addressing include the effect of vaccination on virus change, the different affects of different host species on virus evolution, and the possibility that other unidentified hosts may be present. Until we understand more of these issues, we will be continually playing catch up with the virus and acting in response to rather than in advance of diversification of emerging lineages.

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Table 1

Properties of select H5N1, H9N2, and H3N2 viral lineages

Influenza A virus lineage		Primary Host	Other known hosts	Geographic distribution
Swine-like H3N2		swine	turkey human	North America South Korea
HPAI H5N1		multiple avian	other avian swine rodent feline human	Asia, Middle East, Europe and Africa
H9N2	Y280-like G1-like	poultry	other avian swine human	Asia Middle East
		quail		