



## Review

## Connecting the study of wild influenza with the potential for pandemic disease

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## ABSTRACT

Continuing outbreaks of pathogenic (H5N1) and pandemic (SOIVH1N1) influenza have underscored the need to understand the origin, characteristics, and evolution of novel influenza A virus (IAV) variants that pose a threat to human health. In the last 4–5 years, focus has been placed on the organization of large-scale surveillance programs to examine the phylogenetics of avian influenza virus (AIV) and host–virus relationships in domestic and wild animals. Here we review the current gaps in wild animal and environmental surveillance and the current understanding of genetic signatures in potentially pandemic strains.

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**Abbreviations:** HA, hemagglutinin; NA, neuraminidase; IAV, influenza A virus; AIV, avian influenza virus; PB1, PB2, and PA, polymerase complex; NP, nucleoprotein; M, matrix; M2, matrix 2; NS, non-structural; NEP, nuclear export protein; MatAb, maternal antibody; SA, sialic acid; SGPs, sialylglycopolymers; LPAI, low pathogenic avian influenza; HPAI, high, pathogenic avian influenza; RBD, receptor binding domain; NLG, N-linked glycosylated.

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## 1. Introduction

Nearly 20 years ago, in his landmark review of influenza, Rob Webster pointed out the probability that birds may serve as a source of all influenza A viruses (IAV) that become endemic in other species (1992). The emergence and maintenance of H5N1 lineages in wild and domestic birds and the 2009 novel pandemic strain of H1N1 virus with avian origins in humans have reinforced this view, yet shown the origin of epidemic virus to be complicated (Neumann et al., 2009; Shortridge et al., 1998). In many respects, recent influenza events emphasize the importance of understanding the ecology and evolution of IAV in wild animal vectors and viral reservoir species (Fouchier and Munster, 2009; Melville and Shortridge, 2006; Munster et al., 2007; Normile, 2006). Here, we review the recent literature in influenza with an emphasis on understanding (i) how surveillance research in wild animals and the environment can benefit public health and (ii) on how knowledge of the molecular determinants important in influenza evolution in wild species can inform pandemic preparedness.

Influenza viruses are normally classified by the antigenic properties of their highly variable major surface proteins, hemagglutinin (HA) and neuraminidase (NA). These two proteins are the primary targets of protective immunity in the host. Seventeen subtypes of hemagglutinin (HA: H1–H17) and 9 subtypes of neuraminidase (NA: N1–N9) are described and all but one (H17 in bats (Tong et al., 2012)) and nearly all combinations have been isolated from wild birds (Olsen et al., 2006; Webster et al., 1992) although some more frequently than others. The influenza HA mediates viral binding to host cells and delivery of the viral genome into the cell cytoplasm while the NA assists in viral exit by cutting sialic acid ties to the host cell membrane. The viral genome of eight single-stranded negative sense RNA segments encodes 10+ proteins depending on the strain. In addition to the HA and NA, three proteins form the polymerase complex (PB1, PB2, and PA) and bind the RNA segments with nucleoprotein (NP); matrix (M) and matrix 2 (M2) comprise the protein coat of the virus; and the non-structural (NS) and nuclear export protein (NEP) interact with cellular proteins and processes to assist viral replication and exit and avoid the host immune response. Several additional proteins have been identified in the PB1 and PA segments that are variably present through alternative transcriptional open reading frames, splicing, or secondary start codons. These include PB1-F2 and a suite of recently discovered PA forms (Jagger et al., 2012; Muramoto et al., 2012), all of which seem to impact virulence of infection and which deserve further study.

Since the emergence of a highly pathogenic form of H5N1 avian influenza from a domestic goose in 1997, and its subsequent transmission to humans (de Jong et al., 1997), birds have received increased attention as the source of all natural IAV variants. On

rare occasions, the highly pathogenic forms of IAV have been reported in wild birds – the first outbreak with mortality in wild birds being identified as an H5N3 influenza strain in common terns of South Africa in 1961 (Becker, 1966). However, retrospective analysis has identified avian origins for all segments of human pandemic viruses. This includes the “Spanish flu” of 1918, an H1N1 strain that was perhaps one of the greatest natural disasters in human history and is estimated to have contributed to the death of over 50 million people worldwide. Subsequent pandemic viruses, though less severe, have had enormous impact on human health and include an H2N2 virus in 1957, an H3N2 virus in 1968, and the pH1N1 virus, now endemic, in 2009. Each of these strains resulted from the reassortment of contemporary human strains with viruses derived from birds, but probably delivered through infection of an intermediate host such as the pig. Whether the 1918 virus moved into humans directly from an avian host is controversial. Regardless, the avian origin of all these viruses has spurred research into the avian host in hopes of understanding the characteristics and predictability of pandemic strains at their root.

Domestic and wild birds have been implicated as key agents for interspecies transmission to mammalian hosts of diverse taxa including whales, seals, pigs, horses, and also humans (Claas et al., 1998; Mandler et al., 1990; Reperant et al., 2009; Zhou et al., 2009). Phylogenetic analysis has even revealed that some gene segments belonging to previous human pandemic strains are still circulating in wild bird reservoirs. The NA genes of some H9N2 viruses isolated from migratory ducks in Hokkaido, Japan, clustered with those of H3N2 viruses responsible for causing the human pandemic of 1968 (Liu et al., 2003). Moreover, it has been speculated that the 3 parents of the triple reassortant virus that caused the 2009 H1N1 pandemic may have been assembled in one place by migratory birds (Gibbs et al., 2009). As such, increasing emphasis is now placed on understanding the evolution and molecular determinants of novel and pathogenic forms of influenza that originate from the IAV in birds.

Surveillance research in wild birds holds the promise of informing public health preparedness for pandemic and seasonal influenza. Field surveillance studies to detect avian influenza viruses (AIV) in animal vectors was organized in the early 1970s, culminating with detection of influenza virus from the cloacal swabs of wild ducks (Slemons et al., 1974). Into the 1990s, research in the bird host centred on describing the viral natural history and its maintenance in waterfowl hosts. In response to the threat of Asian origin H5N1, sampling efforts have increased by an order of magnitude or more in the last 5 years, particularly in the US and mainland China (Butler, 2012). These efforts have begun to tie the viral natural history and studies on viral evolution to the potential for generating novel pandemic viral strains. What is clear from past work is that the evolution and natural history of the virus is highly dependent

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