I
fluenza A viruses (IAVs) cause annual epidemics, periodic pandemics, and enzootic infections of numerous animals, including horses, dogs, pigs, seals, and whales (/). The natural reservoir for IAV is wild aquatic birds, including diverse species of Anseriformes (ducks and geese) and Charadriiformes (shorebirds and gulls), which continually transport an incredible array of genetically diverse IAVs over vast distances during migration.

In wild birds, IAVs usually cause apparent, self-limited, lower gastrointestinal tract infections. Such low pathogenicity avian influenza (LPAI) viruses represent most of the avian influenza viruses. IAVs (mostly of low pathogenicity) also occasionally host switch to domestic poultry (mainly chickens and turkeys). Because gallinaceous poultry are not natural hosts of IAVs, sustained epizootic and enzootic transmission in poultry leads to viral genetic changes not found in IAVs adapted to other hosts, such as wild birds or mammals.

IAVs have 1 of 18 hemagglutinin (HA) subtypes (HA being the major surface glycoprotein that elicits immune responses). Two of these subtypes, H5 and H7, can spontaneously undergo mutations at the HA cleavage site to become highly pathogenic avian influenza (HPAI) viruses for gallinaceous poultry, typically resulting in fatal systemic infection in poultry and sometimes in wild birds that come into contact with poultry. We should emphasize that the designation of highly pathogenic and low pathogenicity refers only to bird pathogenicity (i.e., the ability of the virus to cause febrile disease and death). In fact, such viruses can cause symptomatic or severe disease.

Although LPAI poultry epizootics may not be recognized because infections are asymptomatic, fatal HPAI outbreaks in domestic chicken and turkey flocks are obvious and have been described worldwide for >225 years. An Asian lineage of HPAI H5N1, designated A/goose/Guangdong/1/1996 H5N1, emerged in 1996 and has since spread throughout much of Asia, Europe, the Middle East, and Africa, causing almost 900 serious human infections and >400 deaths. This alarmingly high number probably does not represent virulence for or adaptation to humans but rather the existence of rare host susceptibilities to IAVs, considering that millions of persons have been exposed (2).

In the past 2 decades, this H5N1 lineage has developed into multiple sublineages and has undergone multiple rearrangement events leading to major alteration of internal genes but until recently has retained its original N1 subtype neuraminidase (NA).

During 2013–2015, a sublineage of HPAI H5Nx, referred to as clade 2.3.4.4, which had first been reported in 2008 in China, suddenly spread explosively to birds in much of the rest of the world (3,4). In doing so, this sublineage underwent genetic reassortment with various naturally occurring LPAI viruses and repeatedly switched out its long-stable N1 subtype for importations of several new NA subtypes, including N2, N3, N5, N6, and N8. This unprecedented series of events resulted in multiple so-called H5Nx viruses (i.e., H5 clade 2.3.4.4 viruses coupled with any NA subtype that reassorted into the preexisting complex of viral genes). During 2013–2015, H5Nx viruses spread panzootically outward from China (5). Exported H5N6 viruses predominated in Asia, and H5N8 viruses were exported in independent sublineages westward to Europe and eastward to North America. In North America, H5N8 virus reassorted into H5N1 and H5N2 viruses, spreading in early 2015 to 21 states in the United States and causing the loss of >50 million poultry, at a cost of $5 billion. After ≈6 months, these viruses all but disappeared from North America and reseeded dramatically in Europe. In southern China, however, H5N6 has become so widespread in duck populations that it has largely replaced H5N1 as the dominant AIV seen in poultry markets (4).

During summer 2016, H5N8 clade 2.3.4.4 viruses once again began spreading explosively in a second panzootic wave along migratory bird pathways from Russia/Mongolia, separately into Europe and North Africa, the Middle East, and India (6). At the same time, H5N6 clade 2.3.4.4 viruses continue spreading throughout Asia, and there are fears that North America will experience similar resurgent panzootic waves. In the original 2014–2015 panzootic wave, wild bird deaths were uncommon, as is expected for poultry-adapted HPAI viruses. In contrast, the still-ongoing 2016 European/African/Middle Eastern/Indian resurgent panzootic wave has resulted in the deaths of many ducks and a wide variety of wild bird species.

Historically, HPAI viruses are believed to spread by high-production poultry farming and the movements of infected birds, bird material, or surface contamination from infected flocks to susceptible flocks. However, the aggressive
spread of the new HPAI H5Nx viruses in migratory birds along established flyways after breeding and molting sea-
sons strongly implicates migratory wild birds in the 2 recent
panzootic waves. Although genetic bases for panzootic explo-
sivity have not been demonstrated, scientists speculate
that H5Nx viruses have become more transmissible than
other IAVs or more stable in the environment or in wild
birds over long migrations.

In this context, the study of Guo et al. (7) in this issue of
Emerging Infectious Diseases is of particular interest. It
has long been believed that changes in the HA receptor-
binding domain are key to viral adaptation in new hosts,
specifically enabling wild bird–origin IAVs to adapt to do-
mestic poultry, to mammals, and to humans. Avian-adapt-
ed IAVs usually bind preferentially to glycan receptors that
terminate in a sialic acid bound to an underlying galactose
with an α2,3 linkage. NA acts to cleave cell-bound and
virion-bound sialosides, enabling newly formed virions to
be released. Because HA binds sialosides while NA cleaves
them, it has long been assumed that a functional balance is
required between HA and NA activity (4).

Glycan array studies have demonstrated that modifica-
tions to the antepenultimate sugar in these sialosides (e.g.,
sulfation or fucosylation) often affect HA binding affinity.
HA binding to α2,3-fucosylated sialosides, which may be a
feature of galliform poultry adaptation, is likely to be
influenced more widely in both wild bird and in poultry-adapted
IAVs of a variety of HA subtypes.

The study by Guo et al. (7) looked specifically at H5
clade 2.3.4.4 mutations and sialic acid receptor binding
properties associated with emergence and spread of a 2014
European chicken H5N8 virus. The authors report muta-
tions in HA residues 222 and 227 (H3 subtype numbering)
associated with a change in HA receptor binding specificity.
In comparisons of HA glycan array binding properties of an
ancestral H5N1 to those of the newer mutated H5N8 clade
2.3.4.4 virus, the newer HA retained its ability to bind to
nonfucosylated sialosides while at the same time acquiring
the ability to bind to several α2,3 fucosylated sialosides. Ex-
amination of additional H5Nx viruses from wild birds and
domestic poultry is necessary to understand the prevalence
of these binding patterns in H5 clade 2.3.4.4 H5Nx viruses.

The unexpected acquisition of this new property rais-
es several questions. Is the sudden emergence and spread
of H5Nx lineage viruses related directly to fucosylated
sialoside binding, to the blended HA binding specificity
observed, to H5 pairing with new NAs, or to other unap-
nreciated genomic mutations acting alone or in concert?
The founder A/goose/Guangdong/1/1996 H5N1 lineage,
deprive multiple reassortment events over a 20-year period,
did not replace its N1 subtype until the recent emergence of
H5Nx viruses. Did altered receptor specificity for fucosylat-
ed sialosides enable H5 to efficiently partner with a variety
of different NA subtypes that ancestral H5 viruses were
unable to incorporate into their gene complex via reassort-
ment, because of some yet-unappreciated HA/NA func-
tional mismatch? Are the H5Nx viruses more transmissible
or more stable in wild bird species, or more environment-
ally stable? Is the HPAI phenotype expressed differently
than it is with ancestral H5N1 lineages (e.g., in pathogenic
effects on a different spectrum of wild bird species)?

What are the implications for humans, who are not
commonly productively infected by LPAI or HPAI poultry
viruses? Mammalian (and human) adaptation is associated
with non-fucosylated sialosides especially with α2,6-linked
sialoside receptor binding. If enhanced binding to fucosylat-
ed sialosides occurs in these poultry-adapted viruses without
changing the overall binding preference for α2,3-linked si-
aloide (characteristic of galliform poultry adaptation), then
these viruses are presumably less capable of back-adapting to
pose a risk for humans. At the same time, lectin histochemi-
cal studies should be performed to look for the presence and
distribution of fucosylated sialosides along the respiratory
tract of humans, in mammals that either sustain IAV enzootic
spread or that can be infected experimentally (e.g., swine,
horses, ferrets) and in wild and domestic bird species.

How IAVs evolve, switch hosts, and stably adapt to
new hosts remain poorly understood but undoubtedly re-
flects multiple independent pathways. A better understand-
ing of the molecular bases of these host-adaptation events
may help us to recognize genetic signatures of emerging
IAVs that can infect humans, domestic animals, and wild-
life and to better prevent and control transmission.

In addition to providing insight on the mechanisms
by which a novel panzootic virus is emerging, the study of
Guo et al. (7) reminds us of the ability of the influenza
virus to surprise us with a remarkable repertoire of mul-
tidirectional evolution, which presents us with newer and
more complicated challenges. In the past several decades,
influenza viruses have been moving about globally in new
and different ways. If we hope to control them, we need to
understand what they are doing, and how they are doing it.

This work was supported by the Intramural Research Program
of the National Institute of Allergy and Infectious Diseases,
National Institutes of Health.

Dr. Taubenberger is a senior investigator in the intramural
research program of the National Institute of Allergy and
Infectious Diseases, NIH, serving as chief of the Viral
Pathogenesis and Evolution Section and deputy chief of the
Laboratory of Infectious Diseases. His research interests involve
basic and clinical research on influenza viruses.

Dr. Morens is an infectious disease epidemiologist and
virologist. He serves as senior advisor to the director, National
Institute of Allergy and Infectious Diseases, NIH.
References


Address for correspondence: David M. Morens, NIAID/NIH, Bldg 31, Room 7A-03, 31 Center Dr, Bethesda, MD 20892-2520, USA; email: dm270q@nih.gov

December 2011: Zoonotic Infections

- Risk for Rabies Importation from North Africa
- Transmission of Guanarito and Pirital Viruses among Wild Rodents, Venezuela
- Hepatitis E Virus in Rats, Los Angeles, California
- Enterovirus Co-infections and Onchomadesis after Hand, Foot, and Mouth Disease, Spain
- Experimental Infection of Horses with Hendra Virus/Australia/Horse/2008/Redlands
- Lineage and Virulence of Streptococcus suis Serotype 2 Isolates from North America
- West Nile Virus Infection of Birds, Mexico
- Isolation of Prion with BSE Properties from Farmed Goat
- Candidate Cell Substrates, Vaccine Production, and Transmissible Spongiform Encephalopathies
- Molecular Epidemiology of Rift Valley Fever Virus
- Novel Multiplexed HIV/Simian Immunodeficiency Virus Antibody Detection Assay
- Astroviruses in Rabbits
- Host Genetic Variants and Influenza-Associated Mortality among Children and Young Adults
- Severe Human Bovacvirus Infection, Germany
- Continuing Threat of Influenza (H5N1) Virus Circulation in Egypt
- Hepatitis E Virus Antibodies in Blood Donors, France
- Human Cardiovirus, Meningitis, and Sudden Infant Death Syndrome in Children
- Seroprevalence of Alkhurma and Other Hemorrhagic Fever Viruses, Saudi Arabia
- Knowledge of Avian Influenza (H5N1) among Poultry Workers, Hong Kong, China
- Human Liver Infection by Amphimerus spp. Flukes, Ecuador
- Genogroup I and II Picobirnaviruses in Respiratory Tracts of Pigs
- Aedes aegypti Mosquitoes Imported into the Netherlands, 2010
- Animal Diseases Caused by Orbiviruses, Algeria
- Fatal Outbreak of Mycoplasma capricolum Pneumonia in Endangered Markhors
- African Swine Fever Virus Caucasus Isolate in European Wild Boars
- Novel Syltamic Rabies Virus Variant in Endangered Golden Palm Civet, Sri Lanka
- Rickettsia parkeri in Amblyomma maculatum Ticks, North Carolina, 2009–2010
- Japanese Encephalitis Virus Genotype Replacement, Taiwan, 2009–2010
- Altitude-dependent Bartonella quintana Genotype C in Head Lice, Ethiopia
- Proximity to Goat Farms and Coxiella burnetii Seroprevalence among Pregnant Women

http://wwwnc.cdc.gov/eid/articles/issue/17/12/table-of-contents