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Perspective

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Pandemic Influenza Viruses — Hoping for the Road Not Taken

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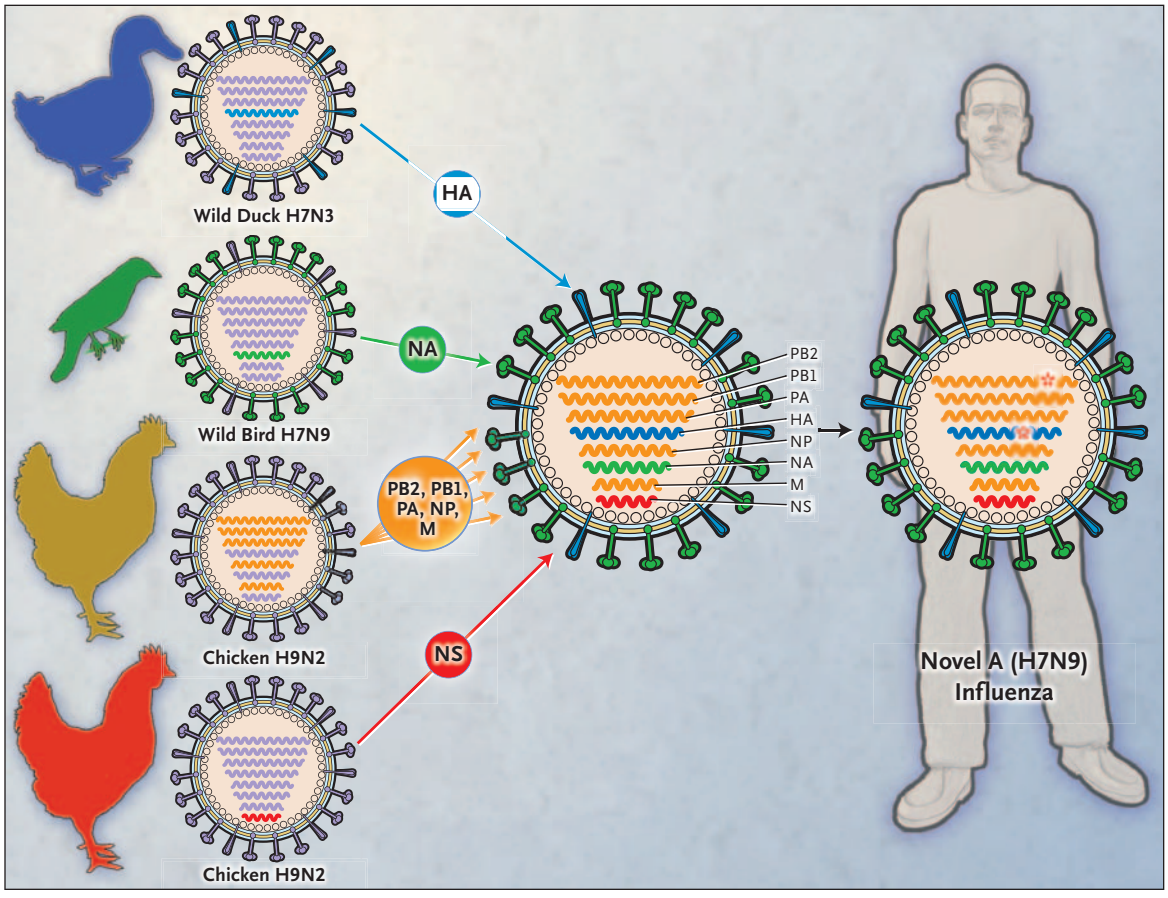
In the Robert Frost poem "The Road Not Taken," a traveler recalls a time when his forest path forked and wonders where he would have ended up had he chosen the other path. Some viruses encounter analogous evolutionary divergence points, and they may not all take linear paths to inevitable outcomes.

For instance, a novel avian influenza A (H7N9) virus has emerged in China.[1] Because all known pandemic and other human, mammalian, and poultry influenza A viruses have descended from wild-bird viruses, it seems logical that any avian influenza A virus that becomes pandemic must have serially acquired signature mutations known to be associated with circulation in humans. It would follow that mutations distinguishing "avian-like" from "human-like" viruses must be milestones on a fixed evolutionary pathway to potential pandemicity, including mutations affecting the hemagglutinin (HA) receptor–binding domain associated with efficient binding to human epithelial cells, polymerase mutations associated with efficient replication in human cells, and others. The fact that H7N9 isolates have some of these mutations[1] has led to predictions of its evolution toward pandemicity.

However, firm scientific evidence for such well-defined linear pathways is lacking. Since 1918, the emergence of four pandemic viruses has been documented, but scientists have found no evidence of a direct mutational mechanism[2]; conversely, many avian viruses have infected humans and rapidly developed such mutations without becoming pandemic. Rather than being indicators of inevitable pandemic progression, these mutations may simply be markers that any avian influenza virus is likely to develop when it replicates in human cells. In keeping with this interpretation, novel human H7N9 isolates have several "human-like" mutations affecting HA, viral polymerase, and other proteins, whereas temporally and geographically related avian H7N9 isolates do not.[1]

The critical but currently unanswerable question is whether every avian influenza virus capable of infecting humans can acquire serial pandemic-generating mutations without being limited by structural or functional evolutionary constraints — or whether pandemic viruses are rare entities whose complex gene constellations cannot easily be configured except by rare and still-obscure mechanisms. We do know that humans, who can be easily infected with avian influenza A viruses by experimental challenge, are naturally and repeatedly exposed to and often infected by many such avian viruses without generating pandemics — as evidenced by multiple epidemics and case clusters as well as by serosurveys.[3,4]

Given the potential daily exposures of millions of humans to various avian influenza viruses,



Origin of the Novel Avian Influenza A H7N9 Virus.

On the basis of published sequences and phylogenetic analyses, it has been hypothesized that the novel avian H7N9 influenza virus is a reassortant virus containing gene segments derived from four separate avian influenza viruses,[1] including two different wild-bird viruses contributing the H7 hemagglutinin (HA) (closest match to wild-duck virus) and N9 neuraminidase (NA) (closest match to a wild-bird isolate) gene segments, and two different domestic-poultry–derived H9N2 viruses contributing the other six "internal" genes (polymerase PB2, PB1, and PA genes), the nucleoprotein (NP) gene, and the matrix (M) and nonstructural (NS) genes. The avian origin of each of the eight H7N9 gene segments is coded by color. A representative H7N9 human isolate is marked with asterisks in the polymerase PB2 and HA genes to indicate key mutations associated with human adaptation.

the extreme rarity of new viral adaptation to humans suggests that despite a low species barrier for infection, barriers against productive infection and onward transmission must be exceedingly high. The reason may be that to adapt fully to humans, avian influenza viruses require precisely attuned and mutually cooperating gene constellations, which result from finely balanced polygenic mutations[4] that are extremely unlikely to accumulate and survive in preadapted viruses.

Moreover, among the 17 influenza HAs and 10 neuraminidases (NAs) known to exist in nature, only a few subtype combinations — H1N1, H2N2, and H3N2 — have ever, in 95 years of virologic observation, been incorporated into any human-adapted or pandemic influenza A virus. Epidemiologic and archaeserologic evidence arguably extends this HA subtype restriction back to the 1830 and 1889 pandemics,[5] supporting the belief that influenza pandemics occur in cycles of H1, H2, and H3 and that this cyclicity is driven by older birth cohorts that retain and newer cohorts that lack high HA-specific population immunity. The apparent HA restriction seems unlikely to be coincidental, since the influenza virus HA genes that have been associated with human pandemic viruses, such as H1 and H2, are not particularly common in avian viruses, and since more common avian influenza subtypes, such as H4 and H6, have never been seen in human-adapted viruses.

If few or none of the millions of avian influenza viruses that continually infect humans ever become pandemic, how do pandemics arise? We know that all

pandemic viruses since 1918 descended from the 1918 pandemic founder virus,[2,5] having been generated through periodic antigenic shifts, intrasubtypic reassortments, and continual antigenic drift.[2] Unfortunately, we do not yet know the origin of the 1918 virus, and phylogenetic and sequence analyses aiming to determine its origin are controversial.

All eight 1918 viral gene segments encode proteins close to the avian influenza A viral consensus sequence, which suggests that they either had a direct avian origin or an evolutionarily brief preliminary period in another host. The relative protection in 1918 of people older than 65, however, suggests that a related virus was circulating after the 1830 pandemic.[5] That possibility is important because if the 1918 virus emerged directly from a bird, then any avian influenza A virus, such as H5N1 or H7N9, might be able to do the same. If, in contrast, it emerged through antigenic recycling, as all subsequent pandemic viruses have done, then it is important to recognize that this pattern has not thus far included viruses with other HAs and NAs, such as H5, H7, and N9. But given influenza viruses' unpredictability, the implications of this historical behavior for H7N9's likelihood of evolving into a human pandemic virus remains unclear.

Although wholly avian in origin, H7N9 seems to have been generated by a reassortment of wild-duck H7 HA and wild-bird N9 NA genes, with six internal genes from two different H9N2 chicken influenza viruses (see diagram). That H9N2 viruses have been spreading panzootically in poultry and have also infected pigs and humans suggests an inherent capacity to adapt broadly to multiple species. This adaptability is worrisome, because H7N9 viruses might theoretically spread with similar ease to encounter other circulating mammalian-adapted influenza genes that are suitable for reassortment. However, host switching of wild-bird influenza A viruses into poultry typically sets off a mutational pathway divergent from mammalian adaptation, arguably driving any such viruses further away from potential pandemicity.[4]

Finally, there is remarkable clinical–epidemiologic similarity between H7N9 and H5N1, with the important distinction that since H5N1 is a highly pathogenic avian virus that kills domestic poultry, its movement is more visible than that of H7N9, whose low pathogenicity keeps it hidden until a rare human is infected. In most other respects, H5N1 and H7N9 are alike: many humans have been exposed to both without clinically apparent or immunologically detectable evidence of infection; disease in sporadic human cases has been far more severe than in cases caused by any human-adapted influenza A virus ever encountered (59% and 28% case fatality reported for H5N1 and H7N9, respectively, as of the end of May); the clinical presentation includes bilateral pneumonia progressing to acute respiratory distress syndrome and multiorgan failure; there has been little or no evidence of person-to-person transmission; and rare case clusters (tenuously identified so far in the case of H7N9) suggest common source exposures in genetically related persons.

As with H5N1,[3,4] in H7N9 these epidemiologic features may be signatures of a fundamentally poorly adaptable avian virus that nevertheless productively infects those rare humans with unidentified genetic susceptibilities, who are "found" by widespread poultry epizootics that expose large human populations. Conceivably, questions raised by H5N1 and H7N9 will be faced repeatedly as large-scale domestic poultry raising and transport, coupled with exploding human populations, create opportunities for any avian virus that encounters domestic poultry to expose large numbers of humans.

Like every human influenza pandemic and major outbreak in more than a century, H7N9 has left us surprised and puzzled. It is only slightly reassuring that since 1918, we have never seen an influenza pandemic emerge through direct viral mutations alone. But every pandemic emergence seems to be a law unto itself, and we cannot know whether or under what circumstances the highly unusual H7N9 virus might be able to become pandemic. Influenza viruses' unpredictability renders H7N9 pandemic preparedness essential. Indeed, preparation has already begun, with the goals of developing sensitive and specific diagnostics; determining drug sensitivity; establishing seed viruses, pilot lots, and potency assays for vaccine development; and setting up clinical trials to test appropriate vaccine doses for various demographic groups (children, adults, the elderly).

H7N9's journey has just begun. We can only hope that the road to a pandemic is the road not taken.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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The H7N9 Influenza Virus in China — Changes since SARS

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Zoonotic infectious diseases are a challenge. Ten years after the emergence in China of the severe acute respiratory syndrome (SARS), another novel virus — an avian influenza A (H7N9) virus — has emerged here, causing substantial disease. These human infections are the first reported cases caused by an H7N9 subtype virus, whose surface hemagglutinin and neuraminidase genes may have derived from H7N3 and H7N9 viruses, respectively, and whose six internal genes may have derived from an H9N2 virus.[1] But China is now alert to potential influenza pandemics and other emerging infectious diseases.

The increasing consumer demand for animal products has resulted in greatly increased animal husbandry and human–animal interactions. The rate of human infections caused by animal pathogens has therefore unavoidably increased, and new infectious diseases have emerged. H5N1 influenza virus, which has caused a total of 45 cases of illness and 30 deaths in humans in China since 2003, was avian in origin.[2] The 2009 pandemic influenza (A/H1N1pdm) virus may have been swine in origin.[3] Now we have identified the novel avian influenza A (H7N9) virus, which within 2 months has caused a cumulative number of human cases in China that is almost three times as high as the number caused by H5N1.

Since the advent of SARS, the Chinese government's awareness of and capacity to respond to health emergencies have substantially improved. The outbreak of the novel H7N9 avian influenza infection has provided us with a chance to evaluate that capacity.

First, rapid disclosure of information has been a priority. The newly established National Health and Family Planning Commission reported to the World Health Organization (WHO) and the public about the epidemic on March 31, 2013, shortly after the Chinese Center for Disease Prevention and Control (CCDC) completed full gene sequencing (on March 29) and the cases were diagnosed (on March 30, after discussion with clinicians and epidemiologists). Since then, information about new confirmed cases has been released on a daily basis.

Second, the overall capacity of the national disease prevention and control system has been greatly improved. The detection and confirmation of the pathogen underlying an emerging disease used to be a complicated and time-consuming process, with special technical requirements. In this case, within 1 month, the novel virus had been identified and diagnostic reagents had been developed and provided for clinical testing.

Third, during the SARS outbreak, the Chinese government's inadequate disclosure of information was due in part to a lack of capacity to collect disease information. A Web-based infectious-disease reporting system has been built during the past decade, and it played a vital role in the response to H7N9. This reporting system, which covers 90% of the township hospitals in China, was put in place at the beginning of 2004. The CCDC receives notification of each clinically diagnosed new case of 39 notifiable diseases from 68,000 computer terminals every day — which may make China's the largest direct infectious-disease reporting system in the world. The government uses the information that the system collects on epidemics, ensuring transparency and the development of proper strategies for addressing those epidemics.

Some observers are concerned that China may not be capable of conducting laboratory diagnosis at hospitals at a grassroots level. In Jiangsu Province, where the economy is more developed than in many other parts of the country, 121 hospitals have been qualified for and are capable of performing nucleic acid testing in suspected cases. It is not practical, however, to enable all township hospitals to undertake such testing.