The Emergence and Control of Zoonotic Influenza – The Present Pandemic Threat

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Introduction

Air travel, internet communication, international interdependence, and the current just-in-time economic organization emphasize that we now live in a “global village.” Although this evolving global organization has many advantages with respect to efficiency, it also has considerable vulnerabilities. Humans are no longer self-sufficient; today’s societal structure is increasingly interdependent. Some natural disasters such as earthquakes and tsunamis can be localized, but their effects on trade and society can be global. Other natural disasters such as infectious diseases have the potential to spread throughout the world, and their overall impact depends on the severity of the infectious agent and the strategies used to mitigate the resulting disease.

The emergence (or reemergence) of infectious agents is a continual process. Recent examples include severe acute respiratory syndrome (SARS), Hendra virus, H5N1 “bird flu,” and the 2009 H1N1 influenza pandemic. Each disease emerged from a zoonotic reservoir (i.e., an animal in which the virus grows and evolves before it is transmitted to other species) and was caused by RNA viruses that evolve rapidly and transmit in an unpredictable manner.

In this session, we will address the effect of potential influenza pandemics on the functioning of societies. We will consider the effect of influenza, its zoonotic emergence, and its potential impact on animal and human health. We will also contemplate the advantages and potential hazards associated with the new field of synthetic biology. Infectious diseases, such as influenza, know no borders and must be considered a global problem; therefore, a global strategy is the solution.

Zoonotic reservoirs of influenza viruses

Influenza is a respiratory infection of humans, horses, swine, dogs, and several avian species, particularly gallinaceous poultry (e.g., chickens, quails, and turkeys). The disease is caused by an RNA virus containing 8 negative-sense RNA segments. The virus belongs to the family Orthomyxoviridae, which consists of 5 genera. The virus expresses 2 major glycoproteins, hemagglutinin (HA) and neuraminidase (NA). HA and NA are important for infection and variation and are embedded in a lipid bilayer that surrounds the RNA segments required for replication and immune avoidance.

The zoonotic reservoir of influenza A viruses are aquatic birds, particularly the Anseriforms (ducks, swans, geese) and the Charadriiformes (shorebirds). To date, 16 HA and 9 NA subtypes of influenza have been detected in this reservoir, where they replicate predominantly in the intestinal tract and are mainly transmitted fecal-orally through water. Influenza causes no apparent disease signs in wild birds, but the virus may influence their initial weight gain and the start of migration. Of the 16 HA subtypes in wild birds, only 3 (H1,
H2, H3) have caused pandemics in humans; 2 (H1 and H3) in swine; and 2 (H3 and H7) in horses. Although many of the HA subtypes replicate in quail, turkey, and chicken and cause moderately severe respiratory disease, only H5 and H7 can evolve into highly pathogenic viruses that spread systemically and kill up to 100% of infected birds.

Influenza viruses frequently transfer from the aquatic bird reservoir to mammals, but infection is usually transitory, and sustained spread is rarely achieved. Multiple molecular changes are required for the virus to move from replicating in the warm intestine of birds (42 °C) to replicating in the cooler respiratory tract of mammals (37 °C). Additionally, the virus must change its receptor-binding characteristics. Intermediate hosts such as swine, which have an intermediate body temperature (39 °F) and possess dual receptor specificity help with this transition.

Evolution of the 2009 H1N1 pandemic influenza virus

The emergence of the influenza pandemic of 2009 surprised influenza experts, because a seasonal H1N1 virus was actively circulating in humans at the time. In brief, the virus emerged in Mexico, not Southeast Asia, which has been hypothesized as the epicenter from which pandemics emerge. Although it was nearly identical antigenically and structurally to the 1918 H1N1 virus, the 2009 H1N1 was comparatively mild. Pregnant women and obese persons experienced the most severe effects.

The virus was a reassortant between the triple-reassortant influenza virus circulating in swine in North America and the avian-like influenza viruses circulating in swine in Europe. It obtained 5 gene segments (PB2, PB1, PA, HA, NP, NS1) from the North American strain and 2 (M and NA) from the European virus. The virus, which replicated deep in the lungs of humans, transmitted rapidly among humans all over the world. The virus also transmitted back to pigs and spread to cats, dogs, turkeys, and ferrets in nature.

In 2011, reassortant influenza viruses were detected in swine in Hong Kong and the U.S. that had disease potential. All 8 gene segments in the pandemic virus were traced back to the avian influenza reservoir, thereby confirming that the wild bird reservoir is the source of genes for all influenza viruses. The virus had been circulating in swine for more than a decade in apparently healthy pigs. Influenza researchers learned 2 important lessons: First, that the severity of an influenza pandemic cannot be predicted based on antigenicity or genotype, and second, that global surveillance of apparently healthy pigs is needed.

Emergence of highly pathogenic H5N1 avian influenza “bird flu”

In May 1996, a child died in Hong Kong due to infection with a highly pathogenic H5N1 avian influenza virus. By the end of 1996, 18 humans had been infected, and 6 had died. These events were unprecedented in the history of influenza infection in humans, and the influenza experts prepared for a catastrophic influenza pandemic. This has not happened, but the threat continues to amplify. Since 1996, more than 560 cases of H5N1 avian influenza infection have been diagnosed in humans, and more than 50% were fatal.

The H5N1 virus has become endemic in domestic poultry in multiple epicenters, including Southeast Asia, Indonesia, and Egypt. The virus continues to evolve, and 12 clades have been identified. In gallinaceous poultry, the virus is 100% lethal, but in some wild and domestic ducks, the virus causes no apparent disease and is shed and spread silently. There is concern that 1 clade (clade 2.3.2) is perpetuated in wild migratory waterfowl.
The H5N1 virus has not yet consistently transmitted between humans, nor has it spread to the Americas or Australasia. However, reassortants between H5N1 and seasonal H3N2 viruses with increased pathogenicity in animal models have been generated experimentally. The H5N1 virus is susceptible to neuraminidase inhibitors, but it requires longer treatment duration than other strains. The concern is that as long as the highly pathogenic H5N1 continues to circulate in domestic poultry, it has the potential to acquire high transmissibility in humans and thus cause a catastrophic global pandemic.

**Synthetic biology of influenza viruses**

The development of reverse genetics for generating infectious influenza viruses and the simplification of the 8-plasmid system now permits influenza viruses to be “made to order.” In 2005, Jeffrey Taubenberger and colleagues published in Nature the complete genome of the 1918 influenza virus. They successfully sequenced all RNA segments of the virus in tissue blocks of deceased servicemen and lung samples taken from an indigenous woman exhumed from the permafrost in Brevig Mission, Alaska. Based on the complete sequence of the 1918 virus and using reverse genetics, scientists regenerated the 1918 influenza virus; the resulting virus is highly pathogenic in mice and macaques. These studies have established our ability to synthesize virus in the laboratory and increased our understanding of innate immunity and the so-called cytokine storm associated with the high pathogenicity of the 1918 influenza virus. Synthetic biology holds the potential for good and evil, and the associated risks must be considered.

**Control strategies for zoonotic influenza**

The control strategies for zoonotic influenza can be simply stated—Keep it out or stamp it out. Four primary strategies are to (1) improve biosecurity and education of risk factors; (2) stamping-out with compensation; (3) vaccination as an adjunct to stamping-out; and (4) vaccination as a control strategy but not aimed at eradication.

Living with highly pathogenic avian influenza virus in domestic poultry by the use of vaccination is potentially dangerous both for poultry, pigs and people. The use of vaccine promotes antigenic drift which is the accumulation of genetic mutations in the virus that enable it to escape immune control. Thus, the use of vaccines should be considered an interim strategy aimed at eradication. The vaccine strategies for avian influenza include inactivated influenza virus in oil-emulsion adjuvant, in vitro expression systems including various viruses (poxvirus, bacculovirus, adenovirus, paramyxovirus, avian leukosis virus, and infectious Laryngotracheitis virus), and naked DNA. Of these methods, the inactivated virus in oil-emulsion adjuvant is the most widely used. The main disadvantage of this strategy is that the vaccines are not standardized for antigenic content. All of the strategies can effectively reduce disease signs and decrease the viral load and level of virus shedding, but they rarely provide sterilizing immunity.

**The present pandemic threat**

We know that the next pandemic of influenza will be of zoonotic origin, but we cannot predict the strain or severity of the pandemic. The ongoing development of methods to determine risk assessment may in the future provide this information. Elucidating the genomics of influenza viruses in wild birds has just begun. Perhaps, this approach will identify the molecular markers that indicate whether an influenza virus has the potential to transmit to swine and humans.
Currently, the greatest threat is the highly pathogenic H5N1 virus, but low-pathogenic influenza viruses such as H1N1 can become a pandemic strain. We must also give attention to H2N2, which has also infected humans. Two key sources of potential threat to humans and animals are laboratory escape (e.g., H2N2) and bioterrorism/intentional release. We must think and plan as a global village and recognize that animal health and human health are interdependent.

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