

## Minireview

# Pandemic Influenza and Its Implications for Transplantation

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**Influenza viruses are important infections in transplant recipients. They may lead to complications including viral pneumonia, secondary bacterial infections and graft dysfunction. There has been a recent widespread outbreak of highly pathogenic H5N1 avian influenza among domestic poultry and wild birds along with a number of human cases with severe disease and high mortality. Genetic changes in the H5N1 virus may lead to efficient human-to-human transmission, heralding the onset of the next influenza pandemic. Discussed are the implications that such a pandemic may have on transplant patients. Logical inferences can be made from data on influenza in transplant patients and from experience with other respiratory virus outbreaks. In the event of a pandemic, it is likely that transplant patients will have more severe disease and higher mortality as compared to the general population. Vaccination and antiviral strategies may be less effective in this population. Implications for transplant programs in general are also discussed.**

**Key words:** Avian influenza, pandemic influenza, transplantation

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## Introduction

### **Virology**

Influenza viruses belong to the family Orthomyxoviridae and are causes of significant morbidity in the general population and in transplant patients (1,2). Influenza is classified into three distinct subtypes based on antigenic differences: influenza A, influenza B and influenza C. Influenza A infects a range of species (humans, swine, equine, avian, marine mammals) and is responsible for large pandemics, whereas influenza B and C are generally restricted to human species. Viral nomenclature has been standardized and consists of influenza type, place of initial isolation, strain and year of isolation (e.g. A/HK/156/97) (1,3).

Influenza A viruses are enveloped, single-stranded negative sense RNA viruses with a segmented genome consisting of eight gene segments (3). Two of the most important gene products are the surface glycoproteins hemagglutinin (HA) and neuraminidase (NA). HA is produced by RNA segment 4 and is responsible for host-cell membrane attachment and membrane fusion. The NA is produced by RNA segment 5 and cleaves sialic acid from the cell surface, thereby allowing for cleavage of viral progeny from infected cell surfaces. There are at least 15 antigenically distinct HA types that have been described in influenza A (H1–H15) and at least 9 NA (N1–N9) types. The majority of human diseases are caused by only a few HA (H1, H2, H3) and NA (N1, N2) subtypes.

## Influenza and Transplantation

There is limited prospective data on influenza infections in transplant recipients. However, influenza can be a significant cause of morbidity and mortality in some organ transplant populations. Reported attack rates have varied considerably and are likely due to differences in transplant populations, immunosuppression protocols, exposures, and type and virulence of circulating influenza viruses (2,4).

Complications of influenza infection appear to be common in hematopoietic stem cell transplant (HSCT) and solid organ transplant populations. There appears to be a relatively high rate of progression to viral pneumonia in some reports, especially in lung transplant recipients and HSCT recipients (4). In one study of organ transplant recipients over a 10-year period, the rate of influenza infection ranged from 2.8 cases/1000 person years (liver transplant) to 41.8 cases/1000 person years (lung transplant) (5). Complications including secondary bacterial pneumonia (17%) as well as extra-pulmonary complications, such as myocarditis, and myositis were observed. This is in contrast to a report by Ljungman et al. on 12 influenza cases in renal transplant recipients (6). Only one patient developed viral pneumonia and one had bronchitis. The remaining 10 patients recovered without complications. Severe disease has been commonly reported in HSCT recipients with attributable mortality rates as high as 43% (4).

### **Indirect effects on the allograft**

Influenza (and other respiratory viral infections) may lead to important immunological sequelae resulting in graft

rejection and/or graft dysfunction. This may be secondary to activation of immunological mechanisms, including the upregulation of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-6 and IL-8 (2). Some studies of kidney and liver recipients have reported a high incidence of acute rejection following infection with influenza (4,5). However, while associations between influenza infection and rejection have been reported, a causal relationship has yet to be established. The most suggestive data is in lung transplant recipients, in whom community-acquired respiratory viruses have been implicated as triggers for acute rejection and for the development of bronchiolitis obliterans syndrome (BOS) (7). In a prospective study of 50 lung transplant patients with community-acquired respiratory virus infections, a higher incidence of acute rejection and BOS was observed when compared with controls without such infections (8). The overall rate of progression to viral pneumonia in these patients was 8%, but was predominantly observed in patients with influenza and para-influenza but not in those with coronavirus or rhinovirus infections.

## **Evolution of Pandemics**

Influenza viruses undergo antigenic changes at a high frequency. The variability in antigens generally involves changes in the external glycoproteins HA and NA. Minor variability is referred to as antigenic drift; viruses produced by antigenic drift may have substitutions in the antibody-binding site and may cause re-infection and epidemics. Larger changes may occur by reassortment of the segmented genome when two influenza viruses simultaneously infect a host cell, producing a virus with new subtypes of surface proteins (9,10). This 'antigenic shift' is responsible for pandemic influenza in a naïve population. Pandemic influenza may also arise due to a direct mutation of an avian virus into one capable of efficient human-to-human transmission, as described in Figure 1 and below (9,10).

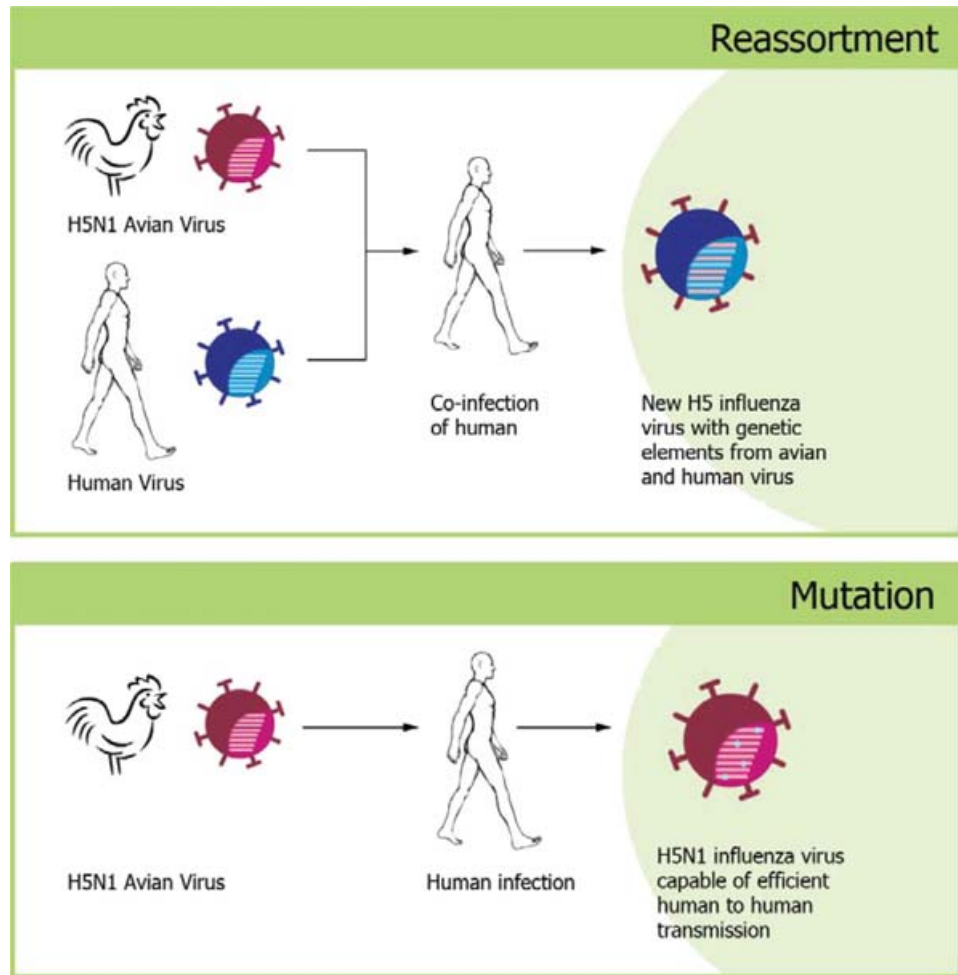
In the past century, three pandemics of human influenza occurred in 1918, 1957 and 1968 (Figure 2) (11). Of these, the 1918 pandemic resulted in the greatest loss of life, estimated at 40 million worldwide. Influenza virus from the last two pandemics emerged as a consequence of reassortment events between two viruses (9–11). In the 1957 pandemic, a reassortment event involving an avian H2N2 and human H1N1 viral co-infection resulted in a transmissible pathogenic new human influenza virus that contained the avian HA and NA genes, and one of the avian polymerase genes. The 1968 pandemic influenza virus appears to have originated from a similar reassortment event that resulted in a transmissible H3N2 virus. Recent data show, however, that the highly virulent 1918 pandemic influenza virus ('Spanish flu virus') did not arise from similar mechanisms. Taubenberger et al. (12) recovered RNA fragments from paraffin block and frozen tissue of patients who died in the 1918 pandemic. By assembling and characterizing the se-

quences of the eight gene segments from this virus, they have shown that the 1918 highly virulent pandemic virus was an H1N1 virus, in which all eight genes appear to be of avian origin. This data suggests that the 1918 virus resulted from cross-species infection from an avian species to humans, with subsequent adaptation of this avian virus to allow for efficient human-to-human spread. Remarkably, only a 10-amino acid difference was found between the polymerase proteins and the avian influenza consensus sequence. Tumpey et al. (13) used reverse genetics to reconstruct the virus and demonstrated that the 1918 virus is 100 times as lethal in mice as any other human influenza virus.

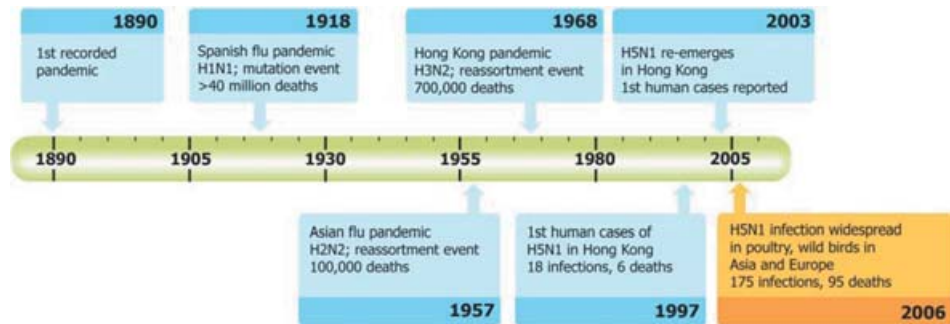
The next pandemic will have several important differences with previous ones. The ease of travel across the globe will facilitate rapid spread. On the other hand, rapid exchange of information, modern molecular tools, antiviral prevention and treatment strategies, and emergency preparedness will help mitigate the pandemic. Another important difference is the increasing numbers of people with compromised immune systems. This includes organ and stem cell transplant patients, and those with other forms of immune compromise, resulting in yet another unknown variable in the pandemic influenza story. In fact, the growing population of immunosuppressed individuals in general, is akin to the 'sentinel chicken' concept, and may provide us with an early warning of potential disease outbreaks.

## **H5N1 Avian Influenza**

Avian species are a particularly important reservoir for the spread of influenza. All 15 HA and 9 NA subtypes are maintained in the aquatic bird population, where viral replication occurs in the gastrointestinal tract and virus is shed in feces at high titers (11,14). Although a number of avian influenza viruses have been responsible for occasional human disease, the current outbreak of H5N1 is most concerning in terms of its pandemic potential (15). H5N1 was first recognized as a cause of human disease in Hong Kong in 1997, in connection with a poultry outbreak in live-bird markets (16). A total of 18 human cases occurred with a 33% mortality. After a quiet period, the virus re-emerged in 2003 (17). Since then, the highly pathogenic H5N1 virus has caused unprecedented outbreaks in poultry stocks throughout Asia (18). These outbreaks are in fact the largest and most severe outbreaks in domestic poultry in recorded history. In addition, the detection of virus in migratory birds (19), and the recent spread of the virus to Europe suggest that migratory birds are directly spreading highly pathogenic H5N1 virus. The outbreak of avian influenza (H5N1) through South East Asia and its progressive spread westward have resulted in increasing concern about the threat of a new worldwide influenza pandemic (15). In fact, the WHO has warned that we are now closer to a global pandemic than at any other time since the 1968 pandemic (Figure 2).



**Figure 1. Pandemic influenza virus may arise from one of two mechanisms:** In Figure 1A, a co-infection with an avian influenza virus and a human influenza virus occurs in a human host (or potentially in another species such as swine). A reassortment event results in a new pandemic influenza virus with genetic elements from both the avian and human viruses. In Figure 1B, an avian influenza virus infects a human host. Mutations in the virus occur, and result in a new pandemic virus capable of efficient human-to-human transmission.



**Figure 2. The time-line of different influenza pandemics is shown.** Although outbreaks have undoubtedly occurred throughout history, only more recent pandemics have been well characterized.

As of March 6, 2006, the total number of human cases confirmed by the WHO was 175, occurring in South East Asia, Turkey and Iraq. Human cases have been primarily due to bird-to-human transmission with only limited non-sustained human-to-human transmission (17,20). The disease in humans seems to have an unusually aggressive clinical course with rapid deterioration, primary viral pneumonia and multi-organ failure (17,21,22). Case fatality has been high (95/175 patients or approximately 54%), often despite the initiation of early therapy. Most cases have occurred in previously healthy children and young adults

(17). It has been suggested that an exuberant host pro-inflammatory response may contribute to excessive tissue injury (23). Recent population-based analyses in rural Vietnam have suggested that milder forms of avian influenza may be common, although this needs to be confirmed with seroprevalence studies (24).

Genetic analysis of the 1918 pandemic virus has made it clear that many similarities exist with the current widespread outbreak of H5N1 to domestic poultry and wild birds with sporadic transmission to humans. Eventually,

H5N1 may undergo sufficient genetic changes to allow efficient human-to-human transmission, resulting in the next influenza pandemic (9,10,15). In fact, the H5N1 virus has undergone antigenic changes (drift) since it first emerged in 1997. Specifically, changes to the HA have been shown by sequencing and antigenic characterization of recent isolates as compared to earlier isolates (25). This may represent the process of adaptation of the virus to the human host. The virus also appears to have expanded its host range to other mammals including domestic cats (26). All that appears necessary for the next pandemic is a genetic change sufficient to allow for easy human-to-human transmission.

## **Pandemic Influenza and Transplantation**

While no cases of H5N1 have occurred in transplant patients, and none of the previous pandemics occurred in an era when transplantation and iatrogenically immunocompromised patients were common, logical conclusions about the effect of pandemic influenza with respect to transplant patients and transplant programs can be inferred from (1) existing data about influenza and other respiratory viruses in transplant patients, and (2) data from recent outbreaks of other viral infections.

The following is a logical extrapolation of the effects that a pandemic influenza outbreak may have on transplant patients: First, the post-transplant patient on immunosuppression may be more likely to develop symptomatic disease if exposed to a specific pathogen. Second, more opportunities for exposure may occur, given that transplant recipients are in close contact with the health care system. Third, it is likely that more severe disease with a higher mortality rate may be seen in transplant patients. Finally, it is possible that transplant recipients with pandemic influenza, or other contagious respiratory virus, may shed large amounts of virus for prolonged periods of time, resulting in spread to a greater number of contacts, i.e. the so-called 'super-spreaders' (27). As an example, data in which quantitative severe acute respiratory syndrome (SARS) coronavirus was measured in post-mortem tissue samples demonstrated very high tissue viral loads from a transplant patient when compared with samples taken from a cohort of non-transplant patients (27). Studies evaluating shedding of influenza virus from throat or nasopharyngeal samples also suggest prolonged shedding in transplant recipients. In immunocompetent adults, the majority of patients no longer shed virus by day 5 of the illness (28). In contrast, in a study of allogeneic HSCT recipients with influenza, the mean duration of viral shedding was 7 days (range 2–37 days); and among 44 patients who received no therapy, the mean duration of shedding was 11.3 days (29).

### **Implications for transplant program**

An outbreak of pandemic influenza will undoubtedly have both direct and indirect effects on a transplant program. For

example, during the SARS outbreak in Toronto, closure of the transplant program occurred due to several concerns (30). Transmission of SARS within health care facilities resulted in concerns about recipient (or living donor) safety as a result of admission to the hospital. Finally, with any new disease outbreak, concerns about transmission of infection from donor to recipients are present. Recent cases of West Nile virus and rabies transmission highlight such concerns, but transmission is theoretically possible in the setting of a disease outbreak of avian influenza. While lung transplantation would logically be the most likely setting in which such transmission would occur, virus may be present in other organs. For avian influenza, case reports of extrapulmonary manifestations have included encephalitis and gastrointestinal symptoms (31). Experimental infection of cats with H5N1 demonstrated viral replication in multiple extra-respiratory tissues (32).

However, of greater importance will likely be the inability of transplant programs to operate in the setting of limited resources. Pandemics can cause large surges in the numbers of people requiring or seeking medical or hospital treatment, temporarily overwhelming health services. The CDC predicts that a 'medium-level epidemic' could kill up to 207 000 Americans, hospitalize 734 000, and sicken about a third of the U.S. population. This will lead to issues of resource allocation, especially given the limited number of ventilator ICU beds available at any given time. It is estimated that during an outbreak of pandemic influenza, ventilator capacity would be quickly outstripped very early in the course of the pandemic. High rates of worker absenteeism can also interrupt other essential services, such as health-care delivery, law enforcement, transportation and communications. During past pandemics, attack rates reached 25–35% of the total population. The 1918 pandemic killed at least 40 million people. In the United States, the mortality rate during that pandemic was around 2.5%. Overall, it would be unlikely that a transplant program could remain active even in a limited capacity during the midst of an influenza pandemic. This would mean that in addition to those dying directly due to influenza, loss of life would occur in potential organ recipients who are unable to receive life-saving transplant procedures.

## **Prevention and Treatment Strategies**

### **Vaccination**

A yearly trivalent inactivated vaccine based on circulating influenza strains has been recommended for all transplant recipients (33). The vaccine is produced from virus grown in embryonated hens' eggs, and contains 15 µg each of two circulating strains of influenza A (H1N1 and H3N2) and 15 µg of an influenza B strain. Vaccines elicit a strain-specific response and have reduced efficacy against viruses that have undergone antigenic drift and are ineffective against those that have undergone antigenic shift. Increases in antibody titer are seen in approximately 90%

of healthy adults who receive vaccine (1). However, the immunogenicity of this vaccine in patients on exogenous immunosuppression is questionable. Although somewhat conflicting, data from several studies show that neutralizing antibody response is suboptimal and ranges from 15–86% (34–37). Indeed, influenza may occur despite vaccination in organ transplant recipients (23). One study showed that two doses of influenza vaccine increased immunogenicity from 68% to greater than 80%, although this data was uncontrolled (38). A live attenuated vaccine has been shown to have similar immunogenicity as the inactivated vaccine in young immunocompetent adults (39). This has not been evaluated in transplant recipients primarily, since live vaccines have generally been contraindicated in transplant recipients due to their ability to cause severe disease. There is also no convincing data to suggest that vaccination plays a role in organ dysfunction or is a trigger for rejection (36,40).

### **Pandemic influenza (H5) vaccines**

Currently, there are no influenza A (H5) vaccines available for humans. Highly pathogenic viruses (H5 and H7) are lethal to chicken embryos and cannot be grown in sufficient quantity (41). Mammalian cell lines have been used to culture influenza for vaccines, but due to their high pathogenicity, work with these virus subtypes requires a high level of biocontainment and safety (41). Various strategies to overcome these limitations are being assessed, such as the use of baculovirus-expressed HA, or using reverse genetic systems to generate reassortant strains (41,42). However, conventional surface antigen vaccine candidates have been found to be poorly immunogenic in clinical studies, and use of whole virus or adjuvants may be necessary (41). It has been estimated that after the onset of an avian influenza pandemic, an immunogenic vaccine for wide-scale use may not be available for several months.

### **Antiviral drugs**

Two classes of drugs against influenza A are available: M2 matrix protein inhibitors and NA inhibitors. These drugs may be used either for chemoprophylaxis or for treatment of influenza infections. M2 inhibitors include amantadine and rimantadine. However, the effectiveness of these drugs is limited due to emerging resistance. The H5N1 strains from South East Asia have mutations in the M2 gene that confer drug-resistance (43). The NA inhibitors, zanamivir (inhaled) and oseltamivir (oral) have similar efficacy for prevention of influenza A, including strains that are resistant to amantadine. These drugs work via specific and potent inhibition of influenza NA enzyme activity, which is responsible for cleavage of sialic acid residues and release of viral progeny from infected cells (44). These drugs appear to be safe in transplant recipients and do not appear to interact with commonly used immunosuppressive medications. Retrospective data in transplant populations (primarily HSCT patients) have shown that these drugs are likely effective in reducing progression to viral

pneumonia, reducing viral shedding and reducing mortality (although emergence of resistance during therapy has been reported) (2,4,45).

NA inhibitors are active against H5N1 avian influenza viruses and have been used for treatment of these patients, with successful outcome most commonly observed if therapy is started early. However, strains with high-level resistance to oseltamivir have been isolated from patients with H5N1 who failed to respond to therapy (46). Stockpiling of the drug by countries and organizations is currently underway at considerable expense, with pandemic plans calling for chemoprophylaxis likely to be given to essential persons in an outbreak setting.

## **Summary**

Influenza is an important pathogen in transplant recipients. The current widespread outbreak of highly pathogenic H5N1 avian influenza in domestic and wild birds, and the occurrence of a number of human cases of infection suggest that the next influenza pandemic may be soon approaching. Many similarities exist between the current outbreak and the 1918 Spanish Flu pandemic that resulted in over 40 million deaths worldwide. In the event of a pandemic, transplant patients will likely be uniquely predisposed to serious infection with high mortality. They may shed higher quantities of virus for longer durations, leading to greater contagious potential. Vaccination and antiviral strategies are also likely to be less effective in this population. Finally, it is likely that transplant programs would be unable to continue to remain active in the setting of an influenza pandemic, leading to further mortality for those on transplant waiting lists.

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