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Emerging, Novel, and Known Influenza Virus Infections in Humans

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KEYWORDS

• Influenza • Pandemic • H1N1 • Transmission • Treatment • Epidemiology

INFLUENZA VIRUSES

Influenza viruses belong to the family of Orthomyxoviridae, which are lipid-enveloped, single-stranded, negative-sense, 8-segmented RNA viruses (**Fig. 1**). Of the 3 known serotypes of influenza (A, B, and C), only types A and B cause frequent and occasionally severe diseases in humans. There is only 1 type of influenza B, whereas influenza A has multiple subtypes, characterized by a combination of the 16 known hemagglutinin (HA) and 9 neuraminidase (NA) genes that code for these viral envelope or surface proteins. These proteins play a role in viral entry and egress from human respiratory epithelial cells within which the virus replicates. Of these 16 HA subtypes, 6 have been found in human infections (H1, H2, H3, H5, H7, and H9). It is generally accepted that the human immune response is mainly targeted at the HA protein epitope of the

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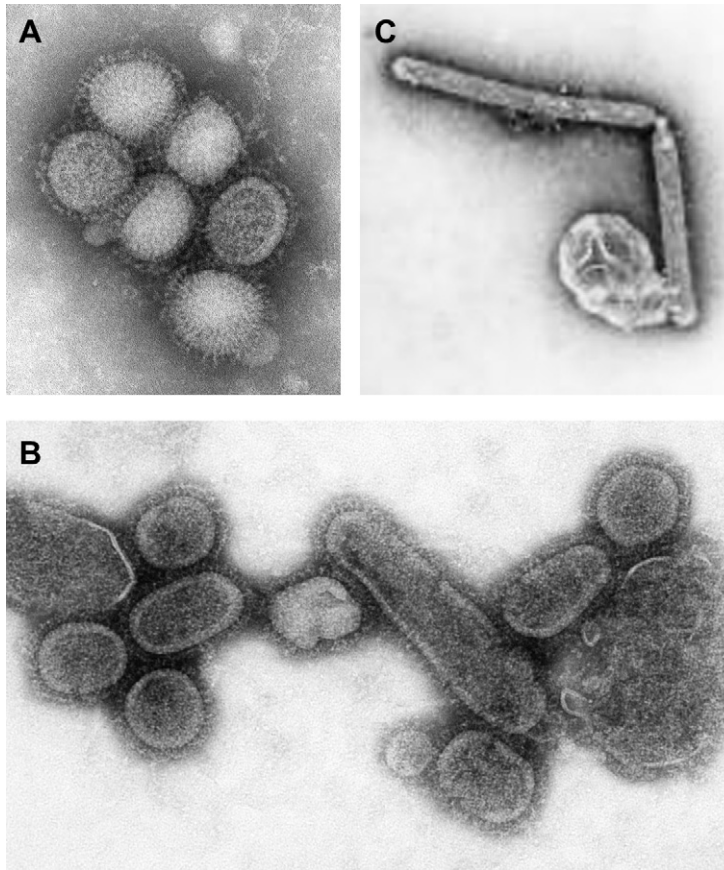

Fig. 1. Negatively stained transmission electron micrographs showing some of the ultrastructural morphology of (*A*) the recently emerged pandemic influenza A (H1N1) 2009 virus of swine origin (strain: A/CA/4/09), (*B*) the recreated 1918 pandemic influenza A (H1N1) virus grown in Madin-Darby canine kidney cell culture, and (*C*) 2 avian influenza A (H5N1) viruses (magnification ×108,000) showing the stippled appearance of the roughened surface of the proteinaceous coat encasing each virion. It should be noted that although these images show different views of these influenza viruses, electron microscopy generally cannot distinguish among the different influenza virus types, subtypes, or strains. (*Data from* The Centers for Disease Control Public Health Images Library. Available at http://phil.cdc.gov/phil/home.asp. Accessed April 17, 2010; #11,212 [*A*], #8243 [*B*], and #8038 [*C*].)

virus, which is why the seasonal influenza vaccine is mainly characterized by its HA (rather than its NA) composition for influenza A.

So far, only 3 subtypes of HA (H1, H2, H3) and 2 subtypes of NA (N1, N2) have caused pandemics in humans. Traditional pandemic surveillance has focused on monitoring the antigenic shift, that is, the reassortment of HA and/or NA genes between human and zoonotic influenza A viruses during rare events of dual infections in a human or an intermediate host. For the surveillance of currently circulating seasonal influenza viruses, most recently the A (H3N2) and A (H1N1) viruses, viral isolates are collected throughout the year to determine the most appropriate seasonal influenza vaccine composition for the coming influenza seasons in the northern and southern hemispheres.

Avian Influenza A (H5N1)

A zoonotic virus (ie, originating from animals and spreading to humans), avian influenza A (H5N1) emerged for the first time in Hong Kong in 1997 from chickens to infect humans, infecting 18 people and killing 6 of them—a high mortality rate of more than 30%.[1]

Originally discovered to be circulating on geese farms in 1996 in Guangdong, China, this highly pathogenic avian influenza A (H5N1) virus soon spread to Hong Kong, causing outbreaks among poultry in 1997. It was eventually eradicated from Hong Kong after a mass cull of all poultry, but it apparently continued to circulate asymptomatically amongst birds in southern China,[2] from where it eventually reemerged in the human population in 2002 to 2003 and has been causing ongoing sporadic human infection and disease, with a high mortality (close to 60%) till present. As of August 31, 2009, the World Health Organization has reported 440 cases of sporadic H5N1 human infection, of which 262 were lethal (a 60% case-fatality rate).[3]

In addition, sporadic, generally mild (although there has been at least 1 recorded death because of H7N7) human infections resulting from occasional bird-to-human transmissions, with low pathogenic avian influenza strains (eg, subtypes H9N2, H7N7, H7N2, and H7N3) have been ongoing since 1997, when heightened surveillance for avian influenza viruses began (**Fig. 2**).[4] So far, all these low pathogenic avian influenza viruses isolated from these sporadic human infections have been genetically similar to the corresponding avian influenza viruses circulating in birds. Thus, so far and within the limits of current surveillance, there seems to have been no further reassortment of these viruses with either human or swine influenza viruses. Until recently, avian influenza A (H5N1) was considered the prime virus subtype candidate for causing the next influenza pandemic.

However, the recent unexpected emergence of the pandemic influenza A (H1N1) 2009 virus (also referred to as H1N1v) of swine origin from Mexico has demonstrated that even influenza subtypes that have been encountered in previous influenza pandemics may constitute new pandemic threats.[5]

INFLUENZA PANDEMICS

Before the emergence of the recent pandemic influenza A (H1N1) 2009 virus, there were 3 pandemics during the twentieth century: in 1918 (the Spanish flu), 1957 (the Asian flu), and 1968 (the Hong Kong flu). These incidents have been widely studied with the help of available (and sometimes extensive) epidemiologic records and any preserved, archived viral isolates or infected tissue specimens.

The first of these pandemics in 1918 coincided with World War I and infected an estimated one-third of the world's population (approximately 500 million people), with approximately 50 million deaths. In contrast, the subsequent 1957 and 1968 pandemics (now shown to have originated in Asia) resulted in a lower morbidity and mortality but still had a significant global effect. Perhaps most importantly, the occurrence of these subsequent pandemics gave rise to the concept that such pandemics could and would recur.

Pandemic influenza viruses are thought to arise when there is frequent human contact with certain animal species that can be infected with their own specific influenza viruses and when these viruses develop the ability to jump the species barrier to infect humans. This crossing is made possible in the presence of certain gene mutations permitting the binding of such animal influenza viruses to surface proteins on human respiratory epithelial cell receptors.[6]

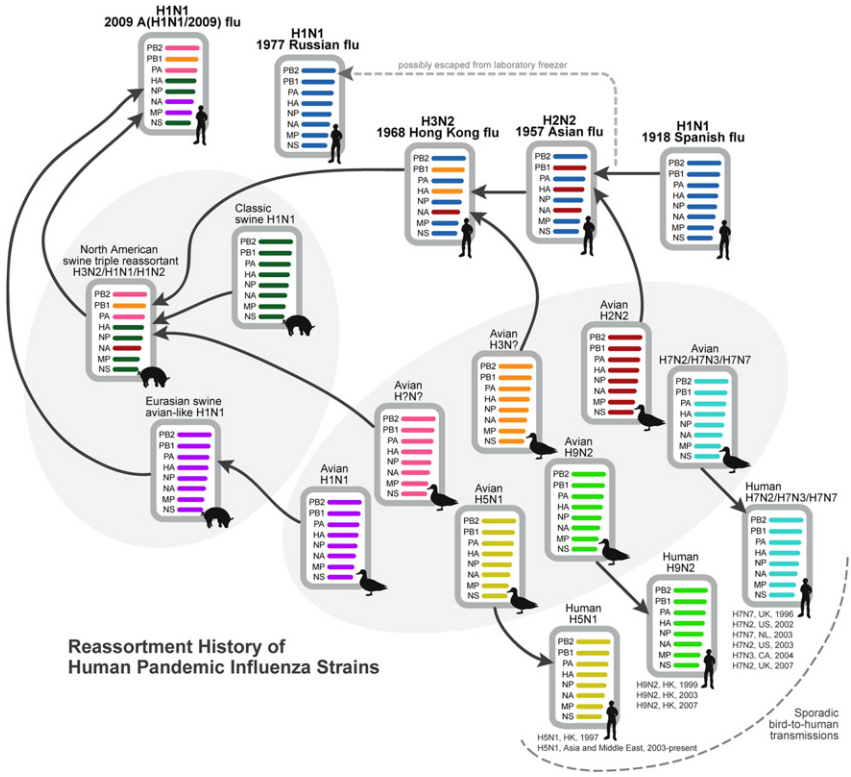

Fig. 2. Reassortment history of human pandemic influenza strains. Each influenza gene segment is represented by a colored horizontal bar. The 1918 Spanish flu influenza and classic swine influenza probably originated from an avian influenza virus population at some point in the past, but arrows indicating their origins have been omitted here because the exact species-crossing events cannot be defined for certain and remain controversial. The reassortment events generating the H3N2 Hong Kong flu pandemic strain have been simplified here because of space constraints. Sporadic bird-to-human transmission events are also shown in the bottom right corner.

Birds are the natural reservoir for influenza A viruses, although other animals such as pigs and horses have also acquired and maintained their own separate genetic lineages of influenza.[7] The origin of the 1918 A (H1N1) pandemic influenza virus has become more controversial recently, and there is a debate over whether it was derived from a human influenza strain existing before 1918,[8] or directly from a purely avian influenza strain from around 1918,[9] or whether it was generated by the reassortment or recombination between human and avian influenza viruses cocirculating around that time. The reason for this controversy is that there are very few viral isolates available for analysis from around this time (before 1918); therefore, the complete diversity of avian influenza viruses circulating then cannot be known.

In contrast, the origins of the 1957 and 1968 influenza pandemics have been more clearly defined (see **Fig. 2**). The 1957 pandemic was caused by an A (H2N2) reassortant strain admixing HA, NA, and polymerase basic protein 1 (PB1) gene segments from avian influenza strains, with the remaining gene segments from the A (H1N1) human pandemic influenza virus subtype that had been circulating since its emergence in 1918.[10] The strain A (H2N2) eventually replaced A (H1N1); then A (H2N2)

was itself replaced by the 1968 A (H3N2) pandemic subtype. The 1968 A (H3N2) virus was also a reassortant strain in which the HA and PB1 gene segments from an avian influenza strain reassorted with the then currently circulating A (H2N2) virus.[10] Since 1977, this A (H3N2) virus has been cocirculating with an A (H1N1) strain similar to the 1918 A (H1N1) pandemic virus, which was accidentally released from a laboratory.[11] Thus, these 2 viruses have now become familiar to us as the seasonal influenza A subtypes for more than 30 years. Analyses of the viruses that caused the 1957 and 1968 influenza pandemics therefore proved that zoonotic transmissions of influenza viruses (ie, from animals to man) with gene reassortment were capable of generating antigenically new influenza strains, novel to human immunity, with significant effects on the public health.

Pandemic Influenza A (H1N1) 2009

The emergence of the first influenza pandemic virus in April 2009 in more than 40 years caught the world by surprise. It was a surprise not just because of the zoonotic origin of the virus (ie, swine rather than avian) but also because of the geographic origins (ie, the Americas rather than Southeast Asia).[12] However, the pandemic preparedness that was already in place to combat the more expected avian influenza pandemic has been used to good effect. The stockpiling of antivirals and a lot of basic and applied research into developing vaccines against novel influenza viruses had already commenced.

Apart from the clinical preparedness, a lot of groundwork has also already been done on the development and application of mathematical models for describing and predicting how the pandemic will evolve,[13,14] as well as identifying and prioritizing public health interventions.[15] This approach has been stimulated greatly by the severe acute respiratory syndrome outbreaks of 2003, and it was easy to apply these techniques to influenza. These mathematical models included not just the traditional epidemiologic models but also the newer approach of phylogenetic analysis applied to partial or whole viral genomes. In some recent analyses of the novel pandemic influenza A (H1N1) virus, this latter approach has been used to give unique insights into the evolution of this new virus.[16]

CLINICAL FEATURES, DIAGNOSIS, AND MANAGEMENT OF INFLUENZA

Case definitions form the cornerstone of the investigation and management of individual patients and outbreaks, although the different influenza subtypes may present in slightly different ways. However, these differences, although statistically noticeable in comparative case series, may not be necessarily useful when faced with individual patients. Ultimately, laboratory diagnosis will always be required to distinguish among the different infecting subtypes.

Clinical Presentation

Seasonal influenza viruses

Clinically, influenza is usually a self-limiting disease. After an average incubation period of around 1 to 2 days, onset of illness is characterized by an abrupt onset of fever and chills accompanied by headache, generalized myalgia, rhinorrhea, sore throat, and cough. Gastrointestinal symptoms such as vomiting, abdominal pain, and diarrhea are often reported. The most common cause of hospitalization is lower respiratory tract infection, including croup, bronchitis, bronchiolitis, and pneumonia. Manifestations involving the central nervous system may be observed, including encephalopathy, postinfluenza encephalitis, transverse myelitis, Guillain-Barré

syndrome, and acute necrotizing encephalitis. Myositis often occurs 3 days (range, 0–18 days) after onset of illness. In young infants, influenza can mimic generalized sepsis. Myocarditis is a rare complication. Epidemiologically, most deaths occur in infants and the elderly (>65 years old) during the annual influenza epidemics as a result of decreased immunity against influenza virus infection. The mortality curve typically presents with a U shape when age-specific excess mortality caused by pneumonia and seasonal influenza is plotted.[17]

Avian influenza A (H5N1) virus

The incubation period for this virus has been estimated to be up to 7 days, but it is more commonly 2 to 5 days after the last known exposure to sick or dead poultry. In cases where limited human-to-human transmission likely occurred, the incubation period was estimated to be between 2 and 10 days.[18]

Analyses of the human A (H5N1) infections in Hong Kong, Vietnam, Thailand, and Cambodia revealed that fever and cough were the most common initial symptoms. Gastrointestinal symptoms including vomiting, diarrhea, and abdominal pain were reported early in the course of illness in some cases.[19] Others reported pleuritic pain and bleeding from the nose and gums. Generally, patients with H5N1 virus infection were hospitalized 4 to 6 days after onset of illness.[18]

Common laboratory findings in patients with A (H5N1) infection at the time of hospital admission include leukopenia, lymphopenia, and mild-to-moderate thrombocytopenia.[19] However, for patients with a clinically mild illness, there was no decrease in the white cell count. Chest radiographic findings included patchy, interstitial, lobar, and/or diffuse infiltrates; consolidation; pleural effusion; and pneumothorax. In fatal A (H5N1) cases, the median time from onset to death was 9 days.[18]

The fatality rate among hospitalized patients has been high and varies considerably between countries (33%–100%), although the true rate maybe much lower because of an unknown number of milder nonfatal infections in the community.[20] Acute respiratory distress syndrome complicated 76.5% (13 in 17) of cases in Thailand and 44.4% (8 in 18) of cases in Hong Kong. Multiple organ failure, with signs of renal dysfunction and sometimes cardiac compromise, was often noted. In the severe human A (H5N1) infections in Hong Kong, reactive hemophagocytic syndrome was a unique pathologic feature in 3 fatal cases, as were increased blood levels of interferon-α, tumor necrosis factor α, and other cytokines, providing evidence that cytokine responses contributed to the pathogenesis of human H5N1 infections.[21]

Exactly how the severity of illness varies by clade or subclade of H5N1 virus infection, by age, or by immunologic, genetic, or other factors is unknown.[18] Most patients who died did not have a preexisting disease, in contrast to situations where other subtypes of human influenza virus infections caused epidemics during interpandemic periods. However, patients with underlying cardiovascular, pulmonary, or renal diseases were, as expected, still more susceptible to severe influenza infection.[20]

Pandemic influenza A (H1N1) 2009 virus

An analysis of 18 cases of pneumonia with confirmed A (H1N1) 2009 infection among 98 patients hospitalized for acute respiratory illness in Mexico City, Mexico, showed that more than 50% of them were between ages 13 and 47 years and only 8 had preexisting medical conditions. All patients had fever, cough, dyspnea or respiratory distress, increased serum lactate dehydrogenase levels, and bilateral patchy pneumonia (**Fig. 3**). Other common findings were an increased creatine kinase level (in 62% of the patients) and lymphopenia (in 61%). Twelve patients required mechanical ventilation, and 7 died. Within 7 days after contact with the initial case patients, a mild

or moderate influenzalike illness developed in 22 health care workers, none of whom required hospitalization.[22]

In a study of 642 confirmed cases of human A (H1N1) 2009 infection identified from the rapidly evolving US outbreak in April 2009, the age of patients ranged from 3 months to 81 years; 60% of patients were 18 years old or younger. Of patients with available data, 18% had recently traveled to Mexico and 16% were identified from

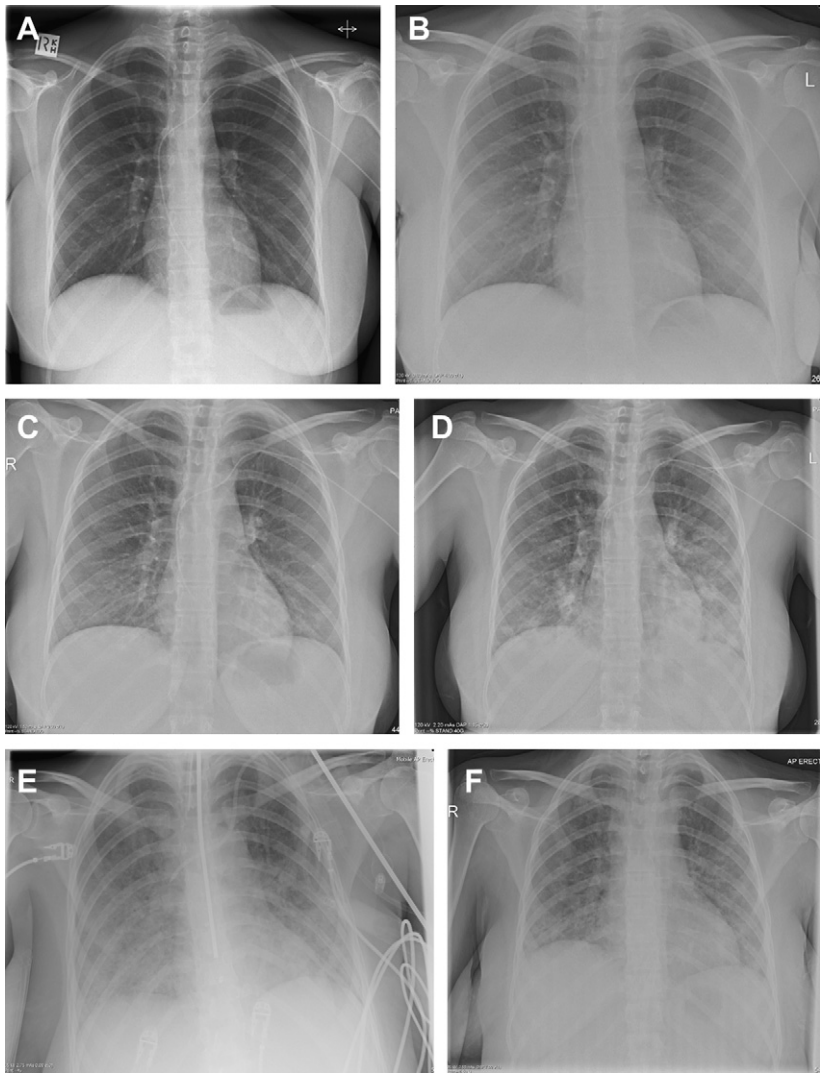

Fig. 3. A series of consecutive chest radiographs showing the progression and final resolution of an adult woman aged 22 years infected with pandemic influenza A (H1N1) 2009. The initial appearance is suggestive of a developing viral pneumonitis, which then seems to resolve (*A*–*C*), but then the patient probably developed a secondary bacterial infection (although not proven conclusively) (*D*) that necessitated a transfer to the intensive care unit (*E*) before finally resolving (*F*). The patient was finally discharged feeling well, with no long-term sequelae. (*Courtesy of* University College London Hospitals NHS Trust, London, UK.)

school outbreaks of A (H1N1) 2009 infection. The most common presenting symptoms were fever (94%), cough (92%), and sore throat (66%); 25% of patients had diarrhea, and 25% had vomiting. Of the 399 patients for whom hospitalization status was known, 36 (9%) required hospitalization and 2 died.[12]

A Canadian study also reported cough in 90% of patients but fever in only 59% of confirmed and probable cases. Other common symptoms included headache (83%), sore throat (76%), and nasal congestion (76%). None of the cases was admitted to hospital. No deaths were associated with the cluster.[23]

It is now becoming clear that most cases of A (H1N1) 2009 infection are mild and self-limiting and present in a manner that is indistinguishable from seasonal influenza. As for seasonal influenza, those with preexisting medical conditions such as the traditional chronic diseases (eg, diabetes, asthma, renal or cardiac failure, and any form of immunosuppression) seem to be at greater risk of severe disease and death (and are therefore routinely targeted for the annual seasonal influenza immunization). Even so, with this virus, it has been suggested that obesity may be an additional risk factor for serious disease,[24] as is pregnancy,[25] which is also a recognized risk in seasonal influenza infection.

The age distribution of infection with this novel virus also differs from seasonal influenza. For example, the older age groups (>65 years) have always been considered to be vulnerable to seasonal influenza infection, but they seem to be less frequently infected by this novel virus. This trend is now thought to be caused by some preexisting cross-reacting immunity to this virus as a result of their past exposure to the older circulating seasonal influenza A (H1N1) strains that have been more similar to the current pandemic A (H1N1) 2009 virus. The current circulating seasonal influenza A (H1N1) virus and its corresponding seasonal influenza vaccine antigen components seem to not provide any cross-immunity to the pandemic strain.[26]

In the more frequently targeted younger adult age groups, an unusual feature has been observed; more patients in this group progress to more serious respiratory disease, whereas there is also a significant gastrointestinal component (nausea, vomiting, and diarrhea in 10%–50% of cases) involved.[12] In addition, in children infected with A (H1N1) 2009, the incidence of seizures seems to be prominent. Although this is also seen with seasonal influenza,[27] the few recent case reports available so far suggest that outcomes are better with the pandemic A (H1N1) 2009 infection.[28]

Antivirals

For all these influenza subtypes, apart from the usual respiratory support and monitoring, there are only a few specific antiviral drugs for treatment. In the cases of seasonal influenza A (H3N2), avian influenza A (H5N1), and pandemic influenza A (H1N1) 2009, virtually all these viruses are resistant to treatment with the adamantane drugs (amantadine and rimantadine) but still susceptible to the NA inhibitors (NAIs) such as oseltamivir and zanamivir. In the case of seasonal influenza A (H1N1), most viruses are resistant to oseltamivir (although zanamivir is still effective in most cases) but still susceptible to the adamantane drugs, although resistance seems to be increasing. Another member of the NAI group, peramivir, is still in clinical trials. Peramivir has an advantage over oseltamivir (taken orally) and zanamivir (taken by inhalation) in that it can be given intravenously. Combination therapy with oseltamivir and rimantadine can be given empirically if the influenza subtype is unknown, and some patients infected with A (H1N1) 2009 have been given this combination as initial empiric therapy.[28]

According to the manufacturer's information, oseltamivir is generally well tolerated and its adverse effects are mild and mainly gastrointestinal (ie, nausea, vomiting,

diarrhea). However, reports from the use of oseltamivir as postexposure prophylaxis (75 mg once daily for 10 days) in primary and secondary school children (age, 4–12 years) have described additional symptoms such as feeling sick, headaches, stomach aches, difficulty sleeping, nightmares, and poor concentration.[29,30]

Table 1 shows the currently recommended NAI doses for treatment and postexposure prophylaxis for patients of different ages. Treatment is recommended for 5 days, whereas prophylaxis is recommended for at least 2 weeks or a minimum of 7 days (eg, at least 10 days as per CDC recommendations in **Table 1**) after contact with the last infected individual and onset of illness. Pediatric dosing is based on weight for those weighing less than 40 kg and older than 1 year. For children younger than 1 year, oseltamivir is not licensed to be administered; however, it can be used on an ''emergency authorization use'' basis, for which the recommended dosing regimen is also shown in **Table 1**. There should be careful monitoring for adverse effects when the drug is used in this younger age group outside its licensure.

The treatment of pregnant women infected with A (H1N1) 2009 is considered a priority, because there seems to be an increased risk (although this is relative) of complications in this population.[25] A recent study suggests that, so far, treatment with oseltamivir appears to be safe in pregnancy[31] and that, on this basis, it should be commenced as soon as possible after the onset of symptoms,[32] as well as being offered for postexposure prophylaxis.[33] However, as always, the actual application of these recommendations is left to the individual decision and risk assessment of the patient and the doctor.

Table 1
Recommended antiviral dosing regimens (for oseltamivir and zanamivir) for the treatment and prophylaxis of influenza A (H1N1) 2009 virus

	Recommended Dose for Treatment	Recommended Dose for Prophylaxis
Oseltamivir (treatment, 5 d; prophylaxis, at least 10 d[a])		
Adults	75 mg twice daily	75 mg once daily
Children aged <12 mo		
<3 mo	12 mg twice daily	Not recommended unless critically ill because of limited data in this age group.
3–5 mo	20 mg twice daily	20 mg once daily
6–11 mo	25 mg twice daily	25 mg once daily
Children aged ≥12 mo and based on weight		
15 kg or less	60 mg/d, divided into 2 doses	30 mg once daily
16–23 kg	90 mg/d, divided into 2 doses	45 mg once daily
24–40 kg	120 mg/d, divided into 2 doses	60 mg once daily
>40 kg	150 mg/d, divided into 2 doses	75 mg once daily
Zanamivir		
Adults	Two 5-mg inhalations (10 mg total) twice per day	Two 5-mg inhalations (10 mg total) once per day
Children	Two 5-mg inhalations (10 mg total) twice per day (7 y or older)	Two 5-mg inhalations (10 mg total) once per day (5 y or older)

[a] As recommended in the manufacturer's fact sheet on oseltamivir for health care providers at http://www.cdc.gov/h1n1flu/EUA/pdf/tamiflu-hcp.pdf.

Adapted from the Centers for Disease Control and Prevention Web site. Available at: http://www.cdc.gov/h1n1flu/recommendations.htm. Accessed August 28, 2009.

Resistance to oseltamivir arising in patients treated with it has been reported in a few cases so far. The most commonly reported resistance mutation, H275Y, occurs in the NA gene.[34,35] The incidence and prevalence of oseltamivir-resistant A (H1N1) 2009 viruses is likely to increase, given the continued widespread use of the drug for treatment. However, oseltamivir should be used for treating only severely ill cases of A (H1N1) 2009 infection (as per seasonal influenza use recommendations) and not for postexposure prophylaxis unless vulnerable groups have been exposed.[32] There has been one case of oseltamivir resistance reported in an individual with no history of oseltamivir use.[36] The issue of worry then is whether such resistant viruses will eventually become fit enough to transmit efficiently in the population (perhaps displacing the wild-type susceptible virus), making the worldwide stockpiles of oseltamivir effectively useless.

Treatment

Antibiotics

There is increasing evidence and conviction that a significant proportion (20%–30%) of deaths caused by past influenza pandemics may have been a result of secondary bacterial infections. Recent analyses of the 1918 pandemic mortality figures suggest that a significant number of deaths were caused by secondary infections with *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and/or *Staphylococcus aureus*.[37] These findings suggest that antibiotics and antibacterial vaccines may be important in the management of influenza infections.[38]

PUBLIC HEALTH ISSUES: PREVENTION AND CONTROL

There are several approaches to prevent infection by the pandemic influenza A (H1N1) 2009 virus, although not all of them are currently available and the evidence supporting the use of some approaches is limited or controversial.

At the individual and population level (ie, in terms of increasing overall herd immunity), immunization with a specific A (H1N1) 2009 vaccine is one of the most effective ways to prevent infection. There are multiple ongoing vaccine trials,[39,40] and recently, a specific live attenuated vaccine (indicated for children and adults, aged 2 to 49 years) has been approved by the US Food and Drug Administration, as of September 15, 2009. Other countries are in the process of approving the vaccine, and it is likely that vaccines against the pandemic influenza virus will be widely available in most countries by the time this article is published. The rapid licensing of this new vaccine has only been made possible by the urgency of the pandemic situation and the application of existing seasonal influenza vaccine manufacturing regulations that do not require annual changes in influenza antigen composition of the seasonal influenza vaccine to undergo relicensing each year. To make the limited supply of these vaccines go further, lower antigenic doses and different adjuvants are being tested to immunize as much of the population as required.[41]

In addition, individual vaccination benefits the population as a whole by reducing the number of susceptible individuals who can be infected by the virus. Given the currently accepted relatively low value for the reproductive number (R_o) of 1 to 2,[13,14] less than 60% (where required vaccine coverage, V_c, is estimated by the formula $V_c = 1 - 1/R_o$) of the population requires vaccination to curtail the onward transmission of influenza. However, there are significant technical (ie, how to make and deliver such a huge amount of vaccine in a short time), moral, and economic (ie, who gets vaccinated first and for what price) challenges that will be faced by the planned global immunization program against the pandemic A (H1N1) 2009 influenza virus.[42,43] With such large

populations being vaccinated, there needs to be careful monitoring for common and rarer (eg, Guillan-Barré syndrome) adverse effects.[44]

Postexposure prophylaxis with oseltamivir for those in close contact with confirmed cases has already been discussed. The disadvantage of mass prophylaxis has been seen in school children when the incidence of adverse effects may be greater than the incidence of secondary infections.[29,30] This situation becomes more relevant with lower estimates of influenza transmissibility (ie, the lower the value of R_o), although this may be higher in certain situations, such as the dense crowding seen in schools and other public entertainment venues.

Simple surgical and N95 masks are probably effective to a certain extent either in preventing the noninfected wearer (eg, health care workers) from inhaling influenza-containing droplets (from either a close or more distant source) or in containing the infectious exhaled air from an infected wearer (eg, patients). The problem with wearing masks for either purpose tends to mainly be that of

Box 1
Nonpharmaceutical public health interventions

Human surveillance

- Case reporting
- Early rapid viral diagnosis
- Disinfection
- Hand hygiene
- Respiratory etiquettes
- Surgical and N95 masks
- Other personal protective equipment[a]

Community restrictions

- School closures
- Workplace closures
- Cancellation of group events
- International and domestic travel restrictions[b]

Patient management

- Isolation of sick individuals
- Provision of social support services to the isolated

Contact management

- Quarantine[c]
- Voluntary sheltering[d]
- Contact tracing

[a] Gowns, gloves, and protective eye covers.
[b] Exit and entry screening, travel advisories.
[c] Separating exposed individuals from others.
[d] Voluntary sequestration of healthy persons to avoid exposure.
Data from Aledort JE, Lurie N, Wasserman J, et al. Non-pharmaceutical public health interventions for pandemic influenza: an evaluation of the evidence base. BMC Public Health 2007;7:208.

maintaining an effective mask position on the face for long periods of time.[45] Sweating and contact irritation can combine to cause mask displacement or removal (noncompliance). It may be particularly difficult when patients suffering from coughing or sneezing are made to wear masks to contain their infection as a form of infection control.

Social distancing has received much attention because of its potential to mitigate and perhaps even curtail the widespread transmission of pandemic influenza. One well-investigated example of this has been the effects of school closure on the subsequent progression of an influenza pandemic. Various mathematical modeling studies have suggested that, although there may be some delay in the spread of the pandemic from closing schools, this measure will only be effective if the subsequent behavior of children outside the school does not result in a similar number of contacts and that such relative isolation is prolonged during the pandemic period. However, the social and economic disruption for the working parents with such a strategy may be difficult to overcome because at least one parent will have to take time off work to look after young children at home. In particular, school closure has to be part of an overall mitigation strategy, including the treatment and home isolation of infected individuals to reduce further contacts.[15]

Air travel can rapidly transport infections between different destinations around the world and also act as a source for generating new infections within the crowded confines of modern passenger planes. Various mathematical modeling tools have been used to assess the effect of restricting air travel on the spread of pandemic influenza. However, the benefits may be fairly minor and may not be worth the inevitable and serious social and economic disruption this will cause.[46]

The possible nonpharmaceutical public health interventions are summarized in **Box 1**.[47]

SUMMARY

The understanding of how novel influenza viruses arise (usually from animal reservoirs) has increased at an incredible rate assisted by the rapid advances in sequencing technologies and phylogenetic methods. Such understanding allows more effective public health surveillance of seasonal human influenza viruses, as well as candidate pandemic viruses that may cross the species barrier from animals to humans. Development in antiviral drugs for influenza is still slow (compared with rapid advances and the variety in the case of anti–human immunodeficiency virus drugs), but this is counterbalanced by the effective and highly organized and regulated vaccine-manufacturing base that is already in existence for the seasonal influenza vaccines. Unlike infectious agents that infect humans only (such as smallpox and measles), influenza viruses, being zoonotic (with animal and human reservoirs), will continue to pose a persistent and variable threat to human health for the foreseeable future. It is therefore important that systems are in place, in health care institutions and in the general community, to react and adapt quickly to limit human morbidity and mortality caused by this ever-changing pathogen.

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