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Use of vaccines and antiviral drugs in the next influenza pandemic

While waiting for the development of an effective vaccine during the early stages of a pandemic, physicians will be able to rely on the antiviral drugs of oseltamivir and zanamivir.

ABSTRACT: In the event of an influenza pandemic, vaccination will be the main way to prevent spread of the virus. Current techniques for developing a vaccine against a novel virus use genetic engineering to allow rapid adaptation to hens' eggs, the medium in which vaccine virus is mass-produced. The effectiveness of immunization depends on how closely the vaccine matches the pandemic strain, and how immunogenic it is in humans. In the initial stages of a pandemic it is unlikely that an effective vaccine will be immediately available. The only remaining option for treatment and prophylaxis will be the influenza antiviral drugs. Currently, these include the neuraminidase inhibitors oseltamivir and zanamivir. Another drug, amantadine, may be less efficacious, as resistance is now common among influenza strains, including H3N2, H1N1, and H5N1 subtypes. A clinical diagnosis of influenza in a pandemic situation is likely to be accurate in the vast majority of patients with influenza-like illness. To be effective, the drugs must be administered within 48 hours of the onset of influenza-like illness. The earlier the intervention, the better the reduction of illness. Canadian and British Columbia pandemic plans require using antivirals in this way. Supply of antivirals will likely be limited, so medical personnel, essential service personnel, and high-risk patients will get priority, at least for the oseltamivir that is stockpiled by public health agencies.

Pandemic influenza has been associated with both moderate and severe morbidity and mortality.[1] The development of a pandemic requires the introduction of a novel influenza strain that the population of the world has no immunity to, and for that strain to be spread throughout the world until disease incidence reaches a certain threshold level of immunity in the population and abates. In addition to public health containment strategies (e.g., closing schools, restricting travel), there are strategies to mitigate the spread of influenza and its clinical consequences:

- Immunization.
- Treatment and prevention with antiviral drugs.
- Clinical management.

Practitioners should be prepared to optimize the use of vaccines and antiviral agents, and to employ effective clinical management of patients in the event of a pandemic.

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Immunization

Inactivated intramuscular injectable vaccine and live attenuated intranasal vaccine (FluMist—not yet licensed in Canada),[2] can be used to prevent influenza, both with comparable efficacy and side effects.[3] The current influenza vaccines are so-called split vaccines, which contain the hemagglutinin (HA) and neuraminidase (NA) of the most current epidemic subtypes of influenza A and influenza B. The three most likely candidate antigens are mass produced by vaccine manufacturers from viruses grown in hens' eggs. "Seed" strains for this mass production are created by a process called "reverse genetics" and recombination, by which a virus can be constructed in vitro, resulting in a progeny that has the required surface HA and NA antigens (with egg-toxic genes removed) combined with a fast egg-growing "backbone" virus.[4] Since vaccines for influenza were first introduced, the A/PR/8 strain, a very good replicator in fertilized hens' eggs, has been the backbone strain. Egg adaptation has been greatly enhanced by the technology of reverse genetics, and now a seed strain can be made in as little as 4 weeks, whereas previously this took months of egg adaptation. Obviously, rapid vaccine manufacture and distribution in the early stages of a pandemic will be the most critical factor in reducing morbidity and mortality. The World Health Organization has developed a strategy to make this as efficient as possible.[5]

The safety, efficacy, and effectiveness of influenza vaccine have been determined by multiple clinical trials.[6-9] To summarize, illness rates are reduced by approximately 75% to 90% in younger persons, and by 50% in the frail elderly. In the latter group, although vaccine does not prevent infection as it does in persons with more robust systems, it does reduce the severity of illness and results in significantly reduced hospitalization and mortality (by up to 70%),[10] possibly because it stimulates a cell-mediated partial protection.[11] Immunization of infants and small children is recommended by the US Centers for Disease Control and Health Canada because it has been proven to reduce hospitalization in these groups.[12,13]

In the next pandemic, whatever the virus happens to be, vaccine will be distributed to priority groups based on the BC Pandemic Influenza Preparedness Plan. These groups are the same as those who now are prioritized to receive influenza vaccine. In order of priority, they are:

1. Health care workers.
2. Essential service workers and security personnel.
3. High-risk medical patients, such as the frail elderly and individuals with chronic underlying organ diseases.
4. Infants and children under 2 years of age.
5. Healthy adults and older children.

While Canada is expected to be self-sufficient in vaccine manufacturing in the event of a pandemic, there is always the possibility of vaccine shortage. In a recent study, a lower dose (0.1 mL instead of the usual 0.5 mL) of trivalent inactivated vaccine injected intradermally in adults instead of intramuscularly (the same technique used for a Mantoux test), stimulated a protective serum antibody level equal to or better than the 0.5 mL intramuscular dose,[14,15] and possibly also a concomitant cell-mediated response because of the stimulation of potent immune-mediating dendritic cells in the skin.[16] This dose-sparing strategy may be useful in extending the vaccine supply in a pandemic situation.

There are also some encouraging data from avian influenza vaccination of ferrets (animals that are highly susceptible to influenza viruses). These animals were protected from the highly virulent avian strain of H5N1 (A/Vietnam/1203/04) and a different clinical Hong Kong strain of H5N1 (A/Hong Kong/156/97) after vaccination with A/Hong Kong/213/03 (H5N1) genetically engineered virus vaccine, indicating that there was cross-protection against several mutated subtypes of H5N1. This might mean it will be possible to manufacture an effective or partially effective vaccine in advance and stockpile it prior to any H5N1 pandemic.[17]

According to the BC Pandemic Influenza Preparedness Plan, organization and implementation of vaccine administration is to be carried out by each regional health authority. The type and dose of vaccine will depend on what the pandemic virus is. Recent evidence suggests that purified HA protein from the avian H5N1 virus does not elicit a very strong antibody response unless it is given at higher antigen dose and with an adjuvant.[18,19] Such a dose is accompanied by more local skin reaction.[19] Others have suggested that a whole virus vaccine (used until the 1980s) might improve the immune response to H5N1, but no comparative studies have been published yet. The current recommendations for influenza vaccination schedules and doses are in effect for a pandemic until better data on vaccine strength and formulation are forthcoming.

Since a pandemic may occur within the next several years, physicians should take every opportunity to immunize their high-risk patients with pneumococcal vaccine. (An estimated one-third of all deaths from the 1918–19 pandemic were caused by combined viral and bacterial pneumonia and one-third from bacterial pneumonia initially triggered by prior infection with influenza.) Although

pneumococcal polysaccharide vaccine does not reduce the incidence of pneumonia and hospitalization, it is associated with a decrease in mortality due to pneumonia in elderly patients.[20] Pneumococcal vaccination rates in adults in BC at present are inappropriately low.

Antiviral drugs

There are three influenza antiviral drugs currently licensed in Canada: the proton channel inhibitor amantadine (Symmetrel), which targets influenza A only, and the viral neuraminidase inhibitors (NAIs) zanamivir (Relenza; treatment dose 10 mg [two inhalations] b.i.d. × 5 days) and oseltamivir (Tamiflu; treatment dose 75 mg [one capsule] b.i.d. × 5 days), which target both influenza A and B. In a pandemic, it is only influenza A that is of concern. Amantadine resistance has steadily increased in current influenza strains to the point where more than 90% of people are resistant and it is no longer recommended for treatment or prophylaxis in British Columbia.[21] In the next pandemic, the plan at present is to use oseltamivir to treat ill persons, as there will likely not be an adequate supply to provide long-term prophylaxis. The current plan calls for having sufficient supplies (at 10 pills per treatment) to treat 17.5% of the population, or half the expected clinical attack rate of 35%. Priority groups for oseltamivir treatment will be the same as for vaccination, although supplies of oseltamivir are now adequate to treat persons from all risk groups.

Experience so far with the 269 confirmed human cases of avian H5N1 influenza (as of January 2007) is that almost all the strains tested have been susceptible to oseltamivir. Some of the variants are susceptible to amantadine.[22] When using NAIs against human influenza A and B, the drug must be administered within 48 hours (and the statistically significant differences between placebo and NAI are only seen if the drug is started within 36 hours).[23-25] The earlier an NAI can be started after the onset of symptoms, the less illness occurs. For example, oseltamivir given within 12 hours of symptom onset rather than 48 hours has resulted in 3 fewer days of symptoms.[26]

There are no randomized trials of the dose or efficacy of oseltamivir or zanamivir in humans with avian H5N1 influenza, the major candidate virus to cause the next pandemic. Human H5N1 disease has been very severe with a 60% mortality rate in the recognized reported cases.[27] The virus behaves unlike the vast majority of human H3N2 and H1N1 influenza strains. It causes a "cytokine storm," an overstimulation of the immune response that is uncontrolled and deleterious, with severe lung edema and hemorrhage occurring within 1 to 3 days.[28] It may present with diarrhea or an encephalitic syndrome (coma) (or both) even before any respiratory symptoms.[29] Virus can commonly be isolated from the blood as well as stool, which is rare in H3N2 and H1N1 influenza. Almost all cases except for a few small clusters of illnesses in family members have occurred in poultry workers. Human-to-human transmission is not efficient at this time.

The optimal dosage of oseltamivir for effective treatment of H5N1 avian influenza is not clearly established. Animal studies suggest that a higher dose and longer course may be required,[30] possibly because the virus is not confined to the respiratory tract. Since the NAI zanamivir is administered with an inhalation device, this drug may not have any effect against virus at a nonrespiratory site. Oseltamivir is generally well tolerated at the 75-mg twice-daily treatment dosage. Nausea and vomiting occur in 7% of persons, but usually stop in 2 or 3 days. The standard course is 5 days for human A/H3N2, A/H1N1, and B influenza. The oseltamivir regimen for H5N1 avian influenza is not clearly established at this time.

Neither oseltamivir or zanamivir have been studied in pregnancy or in infancy. There is possibly some neurotoxicity of oseltamivir in infants under 1 year of age based on animal studies, and the drug is contraindicated in this age group.[31] Oseltamivir has been used in patients as young as 1 year in a family study of oseltamivir

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postexposure prophylaxis, and in one large treatment trial.[32,33] Current recommendations are that zanamivir be used in pregnant women after risks and benefits are weighed. Little of the inhaled drug would likely reach the fetus. If there is influenza in the family, one strategy is to assure meticulous hand washing of all family members, and to keep the infant at least 3 m away from ill family members, who should all wear an approved mask when in the same room as the infant.

When a first wave of pandemic influenza occurs, it is unlikely that an adequate supply of vaccine will be available soon enough to prevent widespread illness.

How will practitioners know if their patients have influenza and can benefit from oseltamivir? In an influenza pandemic, it is likely that the vast majority of influenza-like illness (ILI) will truly be influenza and not illness due to another type of respiratory virus. There are rapid diagnostic tests and cultures for influenza, but recommending that these tests should be done in all patients would not be practical or cost-effective in a pandemic situation after the circulating virus strain has been well characterized. Cultures are needed to identify any oseltamivir-resistant virus. Physicians should recognize the very ill patient and the high-risk patient as candidates for oseltamivir treatment. As is the case with distributing influenza vaccine, each regional health authority will have to obtain expert advisory input and set up a mechanism for the supply, storage, prescription, and timely dispensing of oseltamivir.

Clinical management

The first task in managing pandemic influenza cases is to confirm the diagnosis and determine whether the patient requires hospitalization. Generally, one should decide this on the basis of "how sick the patient looks," the digital oximeter blood oxygen saturation (usually only available in hospital or triage facilities), the presence of multisystem disease, and the patient's risk category. Ill patients with respiratory distress should be referred to a designated triage/treatment location, if available, for an assessment of the need for hospitalization. Patients not admitted need to be given a mechanism for follow-up if their condition deteriorates. For patients with no live-in support, telephone checks by home care nurses or volunteers with a checklist may be a useful strategy. As yet, there is no strategy in the BC Pandemic Influenza Preparedness Plan to give antiviral drug prophylaxis to family members of an ill person (mainly because of an expected supply shortage), and no plan for grouping or isolating ill persons outside the family dwelling. Antibiotics should be administered only when bacterial pneumonia is strongly suspected. In the case of severe avian influenza this may be difficult to ascertain, as the chest X-ray often shows a "white-out" due to pulmonary edema and hemorrhage. Purulent sputum may be a helpful guide to antibiotic use. Sputum and blood cultures should be done if possible, while keeping in mind that laboratory service may be less efficient because of overwhelming need.

Summary

When a first wave of pandemic influenza occurs, it is unlikely that an adequate supply of vaccine will be available soon enough to prevent widespread illness. As a stopgap measure, oseltamivir and, to a lesser extent, zanamivir will be valuable intervention drugs. However, these drugs must be used with discretion, as the supply may be limited. High-risk patients and essential workers will get priority, and the drug will be intended for treatment, not widespread prophylaxis. The key to most effective influenza management will be a well-organized community plan for triage of ill persons, efficient prescribing of influenza antiviral drugs, and optimization of scarce hospital and community resources. Further waves of illness may be prevented by rapid production of an effective vaccine.

Strategies for influenza treatment and prevention are continually evolving. Extensive research is continuing throughout the world under the auspices of the World Health Organization and other agencies in the hope that new information and technology will enhance and hasten interventions to combat an emerging influenza pandemic.

Competing interests

Dr Stiver has been a member of an advisory board for Hoffmann LaRoche Canada.

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