E D I T O R I A L

Preparing for Influenza Epidemics and Pandemics in the New Millennium

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The computerized world has been making great efforts to prepare for the Year 2000 (Y2K) problem, given the potential for major societal disruption if date-dependent software programs malfunction. On the other hand, pandemic influenza, a pathogen capable of creating far greater societal chaos than the "Millennium Bug", has received relatively little recognition and attention. In contrast to the timing of the Y2K problem, which can be predicted with great precision, we do not know when the next influenza pandemic will strike. Pandemic influenza has occurred at least three times this century, in 1918-19, 1957-58 and 1968-69, and another pandemic could be imminent. The pandemic of 1918-19 resulted in 20-40 million deaths worldwide and 30,000 to 50,000 deaths in Canada. Depending on the virulence and penetrance of infection, pandemic influenza could result in as many as 207,000 excess deaths, 734,000 hospitalizations and economic losses of $167 billion in the United States,[1] and an estimated 9,000 to 51,000 deaths in Canada.

In 1997, an outbreak of influenza A H5N1 in Hong Kong dramatically heightened the public health community's awareness that a pandemic can occur at any time and may possess novel epidemiologic features.[2,3] Influenza A/Hong Kong/156/97 (H5N1)-like viruses had only been known to cause outbreaks in birds but for reasons unknown, had jumped the species barrier resulting in 18 confirmed human cases and 6 deaths. Although the H5N1 viruses lacked the ability to spread efficiently from person to person, there was great concern that viruses with pandemic potential could emerge through genetic reassortment with human influenza viruses circulating in Hong Kong.[4] The speed with which epidemiological events evolved and the large number of issues that had to be handled urgently during the Hong Kong outbreak acted as reminders of the need for contingency planning in the interpandemic period.

The establishment of national influenza pandemic planning committees and the development of contingency plans have been proceeding in various countries (including Canada, U.S., U.K., Switzerland, Australia, Japan, France, Belgium) and at the World Health Organization (WHO) for several years. The WHO pandemic guidelines were first implemented in 1997 during the Hong Kong outbreak and were subsequently revised, taking into consideration the risk assessment (data collection and evaluation) and risk management strategies found to be especially important during the outbreak.[5] The Canadian "Contingency Plan for Pandemic Influenza" was first drafted in 1988 and then revised in 1996 by a working group composed of members from the National Advisory Committee on Immunization (NACI), the Advisory Committee on Epidemiology, the Technical Advisory Committee of Public Health Laboratory Directors and the federal government. Over 20 government agencies and professional groups approved the 1996 draft that outlines the core activities during interpandemic periods and steps to be taken if a new virus strain with pandemic potential is identified. Issues addressed include surveillance, laboratory diagnostic capacity, vaccine requirement, supply, distribution and adverse events monitoring, use of antivirals and information dissemination. Efforts are now required to develop contingency planning at the provincial/territorial and local health department levels. Of the 13 provinces and territories who responded to a recent LCDC poll, 7 have a working group on pandemic influenza contingency planning and a draft contingency plan in place or in development, and two have just started organizing working groups.

Surveillance is critical to ensure early warning of new or re-emerging pathogens of epidemic and pandemic potential. A solid surveillance infrastructure must be in existence during the interpandemic period and contingency plans should be in place for rapid expansion of surveillance activities in the event of a novel virus or a pandemic alert. The Laboratory Centre for Disease Control, Health Canada, coordinates the national influenza surveillance program, FluWatch, with the aim to provide timely data which provide a true reflection of influenza activity in Canada.[6] FluWatch consists of 3 main components: 1) laboratory-based influenza virus identification; 2) influenza-like illness reporting by sentinel physicians; and 3) reporting of influenza activity level by provincial and territorial epidemiologists based on local outbreaks, absenteeism from school and work, laboratory and ILI data. Over 180 family physicians participated in the sentinel surveillance program in the 1998-99 season; efforts are still underway to improve participation and population-based representation. Detection of influenza outside of the normal influenza season usually comes from individual reports or investigations of unusual outbreaks (e.g., summertime outbreaks among cruise and land-based travellers); raising public health and health care provider awareness to investigate early and off season influenza-like illnesses, as well as year-round surveillance activities are needed. Hospital-based monitoring of influenza morbidity and mortality should be considered for the provision of timely information on the severity and impact of epidemics and pandemics. Enhanced surveillance during a pandemic may include surveillance at international travel clinics and of travellers from areas where new influenza strains have been identified. In the global context, increased influenza surveillance in Asia and other densely populated locations where there are opportunities for human-live animal contact may contribute to earlier detection of future pandemic viruses.[7]

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New strides in influenza vaccine technology and antiviral therapy in recent years may also affect the management of future epidemics and pandemics. Vaccines are the principal means available to attenuate the impact of an influenza epidemic or pandemic. With today's egg-based manufacturing process, the first vaccine supplies would not be available for at least 3 months after a pandemic was identified. The emergence of human infections by avian influenza viruses (e.g., influenza A H5N1 and influenza A H9N2) that are lethal to eggs has also boosted efforts to find new ways to mass-produce influenza vaccines.[4,8] These include producing vaccine with existing facilities (e.g., attenuating the effect of vaccine virus on eggs, use of avirulent surrogate viruses) and developing alternative techniques (e.g., cell culture grown virus, DNA vaccines).[5,9] Live attenuated, cold-adapted, intranasally administered influenza virus vaccines have been shown to be safe and efficacious in young children, and may have a role in the prevention of influenza and influenza-related otitis media in this population.[10]

Ensuring a secure vaccine supply during a pandemic is one of the key elements of the Canadian Pandemic Contingency Plan. Increasing interpandemic use of influenza vaccine is the best way to build up manufacturing capacity and the vaccine distribution system, and will make expansion to pandemic levels of vaccination easier to achieve. The National Advisory Committee on Immunization recommends annual influenza vaccination for the elderly and persons of any age with chronic medical conditions; an estimated seven million Canadians fall into these high-risk groups.[11] Although the amount of influenza vaccine distributed in Canada has been increasing in the past two decades, only 4.6 million doses are distributed annually and efforts must be made to further improve public awareness for influenza vaccination.

The only antiviral available in Canada for the chemoprophylaxis and treatment of influenza is amantadine; a related drug, rimantadine, is also available in the U.S. Limitations to the use of these drugs include side effects, lack of activity against influenza B and development of viral resistance. A new class of antivirals, the neuraminidase inhibitors, has been developed using structure-based drug design. These drugs specifically interfere with the action of influenza neuraminidase, an enzyme essential for replication of both type A and B viruses. Zanamivir is the first of these compounds to be licenced in the U.S. for the treatment of influenza A and B, but is not yet available in Canada. In adults, zanamivir reduced the severity and duration, by an average of 1 to 1.5 days, of uncomplicated influenza but further studies are required in populations at high risk for severe disease.[12,13] In a recent clinical trial, zanamivir was 67% efficacious (95% CI:39%-83%) in preventing laboratory-confirmed clinical influenza infection when administered once daily for 4 weeks during influenza season to adults under 65 years of age.[14] Compliance with zanamivir may be an issue as it has to be inhaled; orally administered neuraminidase inhibitors are under development. The target sites of neuraminidase inhibitors are highly conserved and clinical resistance to these drugs has not been recognized as a significant problem to date. However, drug-resistant strains have been produced in the laboratory and there is a report of zanamivir resistance after prolonged use in an immunocompromised child with influenza B.[15] Antivirals should not be considered as the main strategy for prophylaxis against influenza pandemics, in view of the cost, need for individual dosing for amantadine and follow up for those at increased risk of side effects, and the potential for non-compliance.

In summary, at the turn of the 21st century there will be more options for the prevention and treatment of influenza together with new telecommunications advances which can be utilized in the development of global and nationwide integrated surveillance and communication networks. The challenge will be to keep up with these new developments and determine their role in influenza control and prevention programs.

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