Influenza – Expect the unexpected

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Influenza is an acute self-limited febrile illness caused by infection with influenza type A or B viruses, and has been causing cyclical epidemics of febrile respiratory disease for centuries. It occurs in outbreaks in almost every winter season in northern and southern hemispheres. The attack rates vary during these outbreak cycles but have been reported as high as 20% to 40% during the peak period of influenza activity (1). Influenza continues to be associated with significant morbidity in the general population, with the elderly, the very young and patients with comorbid illnesses being particularly susceptible. Significant increases in mortality are often seen during influenza epidemics and the excess mortality is not only a direct result of pneumonitis but also of other cardiopulmonary diseases that may be exacerbated by the influenza virus infection. It has been reported that more than 20,000 influenza-associated deaths occurred during each of nine different epidemics between 1972 and 1992 (2), although this figure has been adjusted to an average of approximately 36,000 deaths/year due to influenza in the United States during 1990-1999 based on different modelling (3). In the past, Health Canada has reported that, on average, 500 to 1500 deaths per year are due to influenza or pneumonia occurring as a complication of influenza. It is acknowledged that many more deaths may occur in people with underlying medical conditions complicated by influenza. After using new modelling, however, Health Canada estimates that the figure may actually be from 700 to 2500 per annum (4). Given the early and somewhat unexpected onset to this year's influenza season, and the reappearance of avian influenza in Asia, it is timely to briefly review the current epidemiology of influenza, particularly with respect to the influenza A Fujian strain which is predominant this season.

Influenza A and influenza B viruses are the two types of influenza viruses which cause human epidemic disease. Influenza A viruses are found in many different animals, including ducks, chickens, pigs, whales, horses and seals. Influenza B viruses circulate widely only among humans. Influenza A viruses are divided into subtypes based on two antigens on the surface of the virus: the hemagglutinin (H) and the neuraminidase (N). There are 15 different H subtypes and nine different N subtypes identified to date, all of which have been found among influenza A viruses in wild birds. The H antigen acts as a site of attachment of the virus to host cells to initiate infection and also to erythrocytes from which its name originally was derived (5). The H antigen contains common and strain-specific antigens and demonstrates antigenic variation. The N antigen contains subtype-specific antigens and also demonstrates antigenic variation between subtypes. The N antigen (also known as sialidase antigen) is a surface glycoprotein possessing enzymatic activity essential for viral replication in both influenza A and B viruses. The N antigen enables the release of newly produced virions from infected host cells, prevents the formation of viral aggregates after release from the host cells, and prevents viral inactivation by respiratory mucous (6,7). It is thought that this enzyme may also promote viral penetration into respiratory epithelial cells and may contribute to the pathogenicity of the virus by promoting production of pro-inflammatory cytokines such as interleukin-1 and tumour necrosis factor from macrophages (8-10).

Wild birds are the primary natural reservoir for all subtypes of influenza A viruses and are thought to be the source of influenza A viruses in other animals. Most influenza viruses cause asymptomatic or mild infection in birds; however, the range of symptoms in birds varies greatly depending on the strain of virus. Infection with certain avian influenza A viruses (for example, some strains of H5 and H7 viruses) can cause widespread disease and death among some species of wild birds but especially affects domestic birds such as chickens and turkeys.

Influenza A virus affecting humans has traditionally been classified into three subtypes based on the H antigen (H1, H2, H3) and two additional subtypes based on the N antigen (N1, N2). However, in the last decade, strains of avian influenza containing other H and N antigenic combinations and which have affected humans have been reported. Avian influenza strains were first reported from Hong Kong (11) during the 1997-1998 influenza season and were shown to be derived from avian sources without genetic reassortment between avian and human influenza viruses (11). This first avian influenza A strain (H5N1) affecting humans occurred exclusively amongst residents of the Hong Kong special administrative region and was associated with six deaths during the 1997-1998 influenza season. However, other recent outbreaks of avian influenza in humans have caused limited disease (12). Two cases of confirmed H5N1 influenza occurred in Hong Kong in February 2003, resulting in one death. An outbreak of H7N7 avian influenza in the Netherlands caused the death of one veterinarian in April 2003, and mild illness in 83 humans. Mild cases of avian influenza A(H9N2) in children occurred in Hong Kong in 1999 (two cases) and in mid-December 2003 (one

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case). Most recently, avian influenza strain H5N1 has been identified in three individuals with severe respiratory illness from Vietnam (12). Although current evidence suggests that these strains of influenza A virus were transmitted bird-to-human and are not efficiently transmitted from person-to-person, it does represent a significant new development in the influenza area.

Since the beginning of October, outbreaks of influenza in a number of countries in Europe and North America have been due largely to A(H3N2) viruses (13). Influenza activity continued to increase during November in Canada, Finland, France, Israel, Norway, Portugal, Spain, the United Kingdom and the United States. In Europe (Ireland, Norway, Portugal, Spain, Switzerland), most H3N2 viruses that have been characterized antigenically so far this season are A/Fujian/411/2002-like; in the United Kingdom, two-thirds of isolates characterized so far are A/Fujian/411/2002-like and one-third are A/Panama/2007/99-like. In the United States, more than 75% of the A(H3N2) isolates are A/Fujian/411/2002-like; the rest are A/Panama/2007/99-like. In Canada, the National Microbiology Laboratory has antigenically characterized 490 influenza strains and over 90% are A Fujian. Of the strains tested to date, 483 (98%) are influenza A viruses, including 456 (94%) A/Fujian/411/02(H3N2)-like, 25 (5%) A/Panama/2007/99(H3N2)-like, one (0.3%) A/NewCaledonia/20/99(H1N1)-like and one (0.3%) H1N2. Seven of 490 (2%) are influenza B viruses (14).

The A/Fujian/411/2002-like strains are considered drift variants of the A/Panama/2007/99 virus, which was included in this year's vaccine (15). Therefore, antibodies produced against the A/Panama/2007/99-like strain do cross-react with A/Fujian/411/2002-like strains, but at a lower level. For example, in laboratory tests of sera from recipients of influenza vaccines currently used in the northern hemisphere, there was on average a 41% lower level in the postimmunization antibody titres to A/Fujian/411/2002-like strains, when compared with the A/Panama/2007/99 vaccine strain. Despite such reductions, the tests demonstrated that 76% of adult and 72% of elderly vaccinees possessed protective levels of antibody (hemagglutination inhibition [HI] titres of greater than or equal to 40) to A/Fujian/411/2002-like strains. (15).

There has been the impression that this year's influenza season is associated with greater morbidity and mortality than previous seasons, particularly in the younger age groups. In the last eight weeks, five deaths in children (two in England and three in Scotland) have been confirmed as due to A/Fujian/411/2002-like virus. (13) Since October, 42 influenza-associated deaths among children younger than 18 years of age have been reported to the Centers for Disease Control and Prevention (16). All patients had influenza virus infection detected by rapid antigen testing or other laboratory testing methods. As of Dec 17, 2003 among the 42 reported deaths, 20 patients (48%) were male, and 21 (50%) were female; the sex of one patient was not reported. Twenty-three (55%) of the children were younger than five years of age, and 13 (31%) were aged six to 23 months. The median age was four years (range, nine weeks to 17 years). Seventeen (40%) of the children had underlying chronic medical conditions but the previous medical status for four children (10%) was unknown. Among the 21 patients who had no underlying chronic medical condition, five had invasive bacterial co-infections, including three caused by methicillin-resistant *Staphylococcus aureus* (MRSA), one by *Streptococcus pneumoniae*, and one by Group A streptococcus. Three children with underlying chronic medical conditions had invasive bacterial coinfections, including one caused by MRSA, one caused by *S pneumoniae*, and one caused by *Neisseria menigitidis*. Influenza vaccination status was available for only seven patients; five (aged one year, 14 months, 20 months, three years, and eight years) were not vaccinated; two (aged 21 months and five years) received one dose of influenza vaccine; however, their previous vaccination history was unknown. Influenza A viruses were isolated from 11 patients (26%); 29 (69%) infections were detected by rapid diagnostic testing or by direct fluorescent antibody testing of respiratory specimens. In two patients (5%), evidence of influenza A virus infection was obtained from postmortem tissue samples. Placing these deaths into context is difficult and further analysis is required. Preliminary evidence from the United States suggests that there may be a slight increase in overall pneumonia and influenza mortality over other years. During the week ending January 10, 2004, pneumonia and influenza accounted for 10.2% of all deaths reported through the 122 Cities Mortality Reporting System (17). This percentage is just above the epidemic threshold of 8.1% for that reporting week in comparison to usual trends (17).

Since the start of the current influenza season, Health Canada has reported two deaths in children with confirmed influenza A infection. Health Canada has also learned of two other child deaths that are suspected to be the result of influenza, but have not been confirmed (18). An examination of the FluWatch Report for the past six influenza seasons reveals some intriguing trends (19-24). The peak of the influenza season varies by year, by province or region and by influenza type (A or B). The previous three influenza seasons in Canada have been very mild with influenza-like illness (ILI) rates collected from sentinel physicians being at or below mean historical values and cases peaking at expected periods. However, the two seasons preceding these were not.

The 1998-1999 influenza season was characterized by peaks in activity between early to mid-January and early March. Almost 90% of the strains were influenza A and over 80% of these were characterized as A/Sydney/5/97-like H3N2. The mean rate of ILI was 33/1000 patients seen each week for the entire season, with rates of less than 10/1000 before week 43 and varying between 10/1000 to 30/1000 until week 52, increasing to between 40/1000 to 50/1000 until week 10 and then declining. The 1999-2000 season peaked at the end of December and influenza A predominated, representing 99.1% influenza strains during this season. The 1999-2000 influenza season was characterized by a single peak of influenza activity in early January, which appeared to spread rapidly from west to east. Of the influenza A viruses, A/Sydney/5/97(H3N2) was the predominant circulating strain in Canada and worldwide. The ILI rates varied between 30/1000 to 60/1000 from weeks 41 to 49 and then increased in mid-December (reporting week 49) from 60/1000 to 150/1000 and remained elevated for six weeks. The peak occurred during the last week of December. The mean ILI rate for the 1999-2000 season was 41 per 1000 patients seen. It is noteworthy that during the 1997-1998 to 1999-2000 influenza seasons, the numbers of laboratory-confirmed case-by-case influenza infections reported to Health Canada were higher than for any influenza season in the period 1978 to 1997. This increase in cases may be partly explained by the increase in influenza surveillance activities and a small

increase in the number of reporting laboratories, but likely also represented an actual increase in influenza activity.

The 2000-2001 season, which was notable for significantly lower than usual activity for all national indicators of influenza activity, including the rate of influenza-like illness, the percentage of laboratory-confirmed cases of influenza and provincial/territorial influenza activity levels, had bimodal peaks, with influenza B peaking during early January and influenza A peaking in February. During the 2000-2001 influenza season, ILI rates were below the mean with the exception of two reporting weeks for the entire season and below the 95% lower confidence interval for all but six reporting weeks. The mean ILI rate was 23/1000 and only twice did the ILI rate reach above 30/1000. There was no prominent peak of activity in Canada and the season reflected a mix of early and prolonged influenza B circulation (68% of identified strains) and late influenza A circulation (32% of identified strains). During the 2001-2002 season, which was also mild and in which influenza A predominated in all provinces and territories, influenza activity peaked during the last weeks of March 2002. During the 2001-2002 influenza season, national surveillance indicators showed that influenza activity reached a peak during the last two weeks of March. Sentinel physicians reported 19 to 58 visits for ILI per 1000 patient visits per week, which was at or below the weekly average for the preceding five influenza seasons.

The 2002-2003 influenza season in Canada was also relatively mild. Sentinel physicians reported rates of ILI per 1000 patient visits per week, ranging between 10 to 40, with an average of approximately 25/1000 which was below the weekly average for the preceding six influenza seasons. National surveillance indicators showed that influenza A activity peaked during the first week of January 2003 (representing 57.5% of identified strains) and that influenza B (representing 42.5% of strains) activity peaked during the last two weeks of March 2003. The characterization of the strains from the National Microbiology Laboratory revealed that the influenza A strains were an antigenic mixture of H3N2, H1N1 and H1N2, with the latter representing approximately two-thirds of the characterized strains. All of the influenza A H3N2 isolates that were characterized antigenically by HI tests were similar to A/Panama/2007/99, the H3N2 component of the 2002-2003 influenza vaccine. However, genetic characterization of 15 A H3N2 isolates revealed that nine were A/Fujian/411/2002-like and six were A/Panama/2007/99-like. All of the characterized influenza B viruses belonged to the Victoria lineage and were similar antigenically to the vaccine strain B/Hong Kong/330/01.

Current data in Canada, the United States and globally indicate that the impact of A/Fujian is still within the expected range observed for previous severe influenza seasons. What may be different is the very early onset of the influenza season which began in Canada in late September and early October, first noted in Saskatchewan and Alberta. Of the tested isolates reported to Health Canada to date almost all are influenza A and over 90% of these strains are A Fujian (24). Rates of ILI of between 10/1000 to 38/1000 during weeks 36 to 40 would be considered unusual and isolations of influenza from this time period would confirm that the season has started early in Canada compared to any season within the last few years. In addition, the ILI rates have varied between approximately 15/1000 to 58/1000 between weeks 40 to 52 (2003) and the weekly rate has exceeded the 95% upper confidence interval of the mean on five occasions from weeks 40 to 50 in comparison to the data from 1996-1997 to 2002-2003. In western Canada there is evidence that the illness has already peaked and is declining rapidly, suggesting that overall the season will be greater in magnitude than the preceding three in Canada, providing there is no major influenza B outbreak, but less than the 1998-1999 and 1999-2000 influenza seasons. What remains to be determined is whether young children, aged zero to four years, had greater attack rates and mortality than in previous years. Typically, rates of ILI in children ages zero to four years are 1.5 to two times higher than the overall mean for ILI reported in Canada each year. For example, in the 2000-2001 reporting season, the mean ILI rate/1000 for children aged zero to four years was 43 compared with an overall mean of 23. The unfortunate deaths of young children with influenza in Canada and elsewhere may not be extraordinary when all of the data is taken into context and with the realization that the past three years have been unusually mild with respect to influenza. Alternatively, with little exposure to influenza virus in the past three years, there would be a dearth of natural antibodies to this strain which has demonstrated drift, in the zero to four years age group, which may make this population more susceptible. The cross protection provided by the current vaccine strain in this age group will also need to be examined in depth. A recently published retrospective cohort study conducted among workers at a Colorado hospital providing preliminary data on the relative lack of effectiveness of this year's trivalent inactivated influenza vaccine against influenza-like illness had many drawbacks and more carefully designed studies will need to be conducted (25). Only additional time and analysis will provide more clarity to the questions posed by the 2003-2004 influenza season. Given the relatively mild influenza seasons for the past three years, it should come as no surprise that with this virus and its history intertwined with humankind, we should expect the unexpected.

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