Pandemic influenza— A primer for physicians

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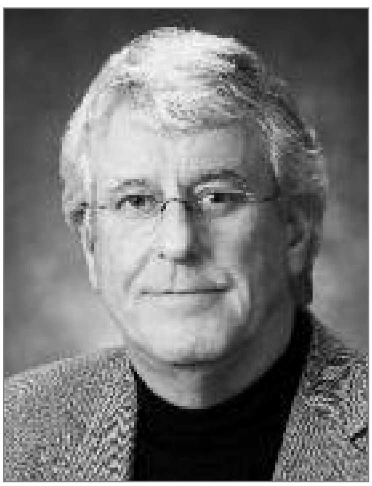

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For this theme issue on pandemic influenza, we assembled a panel of experts and asked them to contribute practical and informative articles on a number of topics. In the first article, Drs Daly, Gustafson, and Kendall provide some history and background on pandemic influenza. Dr Stiver describes the role of vaccines and antiviral drugs, and Dr Gustafson discusses current thinking about public health measures in the event of an influenza pandemic. The other articles all focus on the importance of communication and coordination. Drs Petric and Krajden describe the critical role played by laboratories in the diagnosis of influenza during a pandemic, and Drs Mackie and Lu discuss the need for BC's health authorities to have a strong relationship with physicians. Finally, Dr Daly addresses the importance of physician offices when it comes to planning for a response to pandemic influenza.

Looking back

Pandemics, from the Greek *pan* (all) and *demos* (people), are caused by the emergence of novel pathogens capable of sustained person-to-person transmission through mostly susceptible populations. Pandemics thus represent widespread community outbreaks of serious human illness that affect virtually every country throughout the world. There have been a number of significant pandemics in human history, generally following the domestication of animals or other contact between animals and humans. Examples of zoonotic pandemics include smallpox, plague, tuberculosis, influenza, and more recently, HIV. Severe acute respiratory syndrome (SARS) emerged as a zoonotic infection in 2003 but did not cause a pandemic.[1] Rapid action by health authorities limited the spread of the SARS *Coronavirus* primarily to nosocomial outbreaks in just a few countries.

The virus that causes influenza was identified in 1933, but influenza pandemics long predating this have been identified on the basis of cardinal features of influenza illness, considered "an unvarying disease caused by a varying virus."[2,3] Characterized by febrile catarrhal illness, influenza pandemics have occurred irregularly since at least the 16th century and are distinguished by three classic epidemiological features: their explosive nature (peaking abruptly over 2 to 3 weeks and lasting 5 to 10 weeks), their high community attack rates, and their paradoxically low individual case fatality (or CF, the proportion ill who die as a result).[4-8]

There were three definite influenza pandemics during the 20th century: 1918–19, 1957, and 1968. All three had their origins in avian influenza viruses that transcended the species barrier either directly through adaptive mutation (1918–19) or indirectly through genetic reassortment (1957, 1968).[9,10] Such events are unpredictable, random occurrences and no one knows when another pandemic may occur. Influenza viruses replicate at a rapid and error-prone rate and ecological conditions may now, more than

ever, favor chance pandemic transformation. Modern commercial poultry practices bring susceptible birds, housed sometimes by the thousands, into close proximity with dense populations of susceptible humans. If avian influenza viruses are introduced into that setting, new variants with altered characteristics can rapidly emerge. Unprecedented and expanding outbreaks of avian influenza H5N1 in poultry are a particular concern: since 2003 and as of 3 May 2007, 59 countries on three continents have been affected, with 291 human cases in 12 countries and a striking case fatality of 60% reported, primarily among those having direct poultry contact.[11] While this does not constitute a pandemic, the intrinsically changeable nature of the influenza virus, and links between previous pandemics and avian influenza viruses means the pandemic potential this represents cannot be regarded casually.[11] Other leading candidates for causing a pandemic are H7 and H9 avian influenza subtypes or re-emergence of the H2 subtype which circulated between 1957 and 1968 but disappeared from circulation thereafter.

Together with the plague of Justinian in the 6th century and the Black Death of the 14th century, the 1918–19 influenza pandemic ranks among the most devastating pandemics of any kind—indeed, it has been considered "the greatest medical holocaust in history."[4-6] During that pandemic, 50% of the world's population became infected, with 25% suffering clinical illness.[5,12] Initially, the US population was affected in March, April, and May 1918; subsequently, influenza spread around the world, with many countries in the northern hemisphere experiencing an epidemic during the atypical period of May, June, and July.[4] This first wave was seen as the mild "three-day fever" type of influenza. The second wave was much more severe and began effectively in September or October of 1918 before reaching a peak, in terms of mortality, in October, November, or December.[4] In Australia, reports suggest the second wave did not begin until 1919.[4,13] The third wave of the pandemic was typically much more serious than the first, but was responsible for far fewer deaths than the second.[4]

By some estimates, the influenza pandemic of 1918–19 killed more people worldwide (50 to 100 million) in a matter of months than were killed during all the years of both the First and Second World Wars combined.[4] By comparison, the combined excess mortality for the pandemics of 1957 and 1968 ranged from less than 1 million to 6 million at most.[14,15] During the second and third waves of the 1918–19 pandemic, the CF was less than 5% of all clinical cases; in 1968 the CF was 10-fold less (0.1%).[5] It is estimated that one-third of all deaths in 1918 were caused directly by viral invasion of the bronchi and lung tissue, one-third resulted from combined viral and bacterial pneumonia, and one-third from bacterial pneumonia initially triggered by prior infection with influenza.[15] Seen from another perspective, the reported case fatalities of 1918–19 highlight the fact that virtually all affected persons (>95%) fully recovered as in other pandemics, without the benefit of vaccines, antivirals, or antibiotics. This is reconciled with the staggering death statistics from that pandemic because a low individual risk of dying multiplied by very high attack rates and numbers ill can still culminate in a large absolute number of deaths. Whether a trade-off in virulence toward lower case fatality inevitably accompanies the transition toward enhanced infectivity in humans, and whether this could also apply to H5N1, is unknown.

Because a pandemic will be a civic and economic emergency, as well as a health care crisis, the input of all citizens, including clinicians, is needed for planning purposes.

The pandemic of 1918–19 was also distinguished by the youthfulness of those who died. During annual winter outbreaks, more than 90% of influenza-related deaths occur in the elderly; during the 1918–19 pandemic, more than 90% of deaths occurred in those younger than 65 years and half occurred in young adults. As in other pandemic and interpandemic periods, the peak age-specific incidence in 1918–19 appeared to have been among young schoolchildren 5 to 10 years of age, who themselves suffered among the lowest mortality rates.[16-18] Peak mortality rates in 1918–19 occurred in young adults aged 25 to 29 years, with the next highest rate in persons 30 to 34 years.[18] According to narrative accounts by attending physicians: "Stricken with the same disease at the same time, the chances of a man of 55 pulling through seemed better than the chances of a man of 25 or 30."[19]

High mortality rate in the young adult population is considered a unique feature of the 1918–19 pandemic, but a relative shift in the distribution of excess mortality toward younger persons may be a general pandemic signature.[8] From historical records of the influenza pandemic of 1781, the "middle age" (16- to 45-year-old) patients were also described as having "felt it most" while "children and old people escaped entirely or were affected in a slighter manner."[20] Historical records show that those aged 20 to 40 also accounted for a greater proportion (20%) of influenza-related deaths during the 1890 pandemic in London, England; this declined to about 10% during seasonal activity a decade later, increasing again to 36% during the 1918–19 pandemic.[8] Similarly, during the 1968 pandemic in the UK, 65% of influenza-related deaths occurred among persons younger than 65 but then declined to 10% over the subsequent decade.[8] In the US, persons younger than 65 also accounted for about half of all deaths during the 1957 and 1968 pandemics.[8,16] Current pandemic priority groups for intervention are risk-based with primary reference to interpandemic death rates by age. Interpandemic profiles, however, may not be the best indicators of risk distribution during a pandemic; real-time surveillance for mortality and other serious outcomes will be needed to inform this. About 90% of human cases and nearly 95% of deaths due to H5N1 have occurred among persons younger than 40 years of age. This is a disproportionate concentration of H5N1 infections and deaths in the young, even allowing for the relatively young populations of countries affected. In that regard, youthful patterns of risk observed during previous pandemics may be especially relevant to consider now.[11,21]

Looking ahead

As Canadians, we are fortunate to live in an era and an area where access to modern technologies such as vaccines and drugs are even a possibility during a pandemic. Our challenge in the 21st century will be how to use these technologies in the most effective, efficient, and fair way once a pandemic is declared. Canada is one of the few countries to have established domestic manufacturing of influenza vaccine, and to have protocols in place to evaluate prototype pandemic formulations and to facilitate their efficient review and licensure. Governments across Canada have purchased oseltamivir stockpiles amounting to 55 million 75-mg capsules with a view to the early treatment of 17.5% of the population. Mechanisms for timely distribution are being discussed along with possible, but limited, prophylaxis indications. The prophylactic treatment of just one health care worker will consume about 5 to 10 times the amount of drug required to treat one seriously ill person, and these difficult trade-offs in available supplies must be considered.

It will be tempting to use extreme measures to delay and diminish the intensity of a pandemic, but unnecessary incursions on personal freedoms and societal disruption should be avoided. Mathematical modeling and historical evidence for nonpharmaceutical measures such as respiratory etiquette and isolation, or community interventions such as school and mall closures, or cordon-sanitaire-type quarantines are being scrutinized. The role of schoolchildren in amplifying virus circulation and risk to the community is being assessed. Compliance and contingencies for the care of dispersed cohorts, especially schoolchildren, must also be incorporated.[4] Prioritization of scarce human and material resources and clinical triage will be necessary. Ideally, difficult decisions will be resolved based on previously determined and broadly shared social and ethical principles. Because a pandemic will be a civic and economic emergency, as well as a health care crisis, the input of all citizens, including clinicians, is needed for planning purposes.

Readers who would like further details related to provincial and national level planning for pandemics are encouraged to contact their local health authority or to visit the web sites of the BC Ministry of Health (www.health.gov.bc.ca/pandemic), the Public Health Agency of Canada (www.influenza.gc.ca), where the most recent 2006 version of the national plan can also be found (www.pandemicplan.gc.ca) or the web site of the Canadian Public Health Association (www.pandemic.cpha.ca). Pandemic planning is an iterative process that must accommodate evolving knowledge and understanding. We hope this series of articles will stimulate discussion and inform further progress at all levels.

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