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Introduction to pandemic influenza

We cannot predict when the next pandemic will occur or how severe it will be, but we can estimate overall impact using our knowledge of past pandemics.

ABSTRACT: Influenza pandemics are global outbreaks that result from the emergence of new subtypes of the influenza A virus. A pandemic can occur if a new subtype causes significant human illness and is easily transmitted from person to person. New subtypes may arise from strains of avian or swine influenza A, which can occasionally cause human illness but rarely precipitate pandemics. H5N1 avian influenza, first identified a decade ago, has caused widespread outbreaks among poultry since 2003 (beginning in Asia and then spreading to Europe and Africa) and rare but severe human illness. Concern that H5N1 may mutate to produce a pandemic strain has prompted increased pandemic planning among public health officials worldwide.

Influenza pandemics can cause significant morbidity, mortality, and social disruption worldwide. The history of pandemics shows that a pandemic has occurred every 10 to 40 years over the last 400 years. Recent concerns about widespread outbreaks of avian influenza H5N1 among poultry (accompanied by more than 290 reported and confirmed human cases) have renewed pandemic planning efforts from governments and public health officials. Since influenza pandemics spread primarily in community settings, community physicians will provide much of the health care response during the next pandemic. However, community physicians' involvement in pandemic planning has been limited to date—something that must be addressed so that the needs of physicians and their contribution to pandemic response can be well defined. This will not only help physicians to prepare for the next influenza pandemic, it will provide a good platform for considering the issues facing physicians in other public health emergencies.

Influenza A viruses

Physicians are very familiar with influenza, which in most otherwise healthy children and adults causes a self-limiting febrile illness with fever, headache, myalgias, and cough. Complications can include viral or bacterial pneumonia, exacerbation of underlying conditions such as congestive heart failure, and, occasionally, death. During seasonal influenza, complications affect mostly the elderly, the very young, and those with underlying cardiac and respiratory conditions.[1]

Influenza viruses are part of the Orthomyxoviridae family and are made up of three types—A, B, and C—all of which can infect humans. Type A influenza viruses can also infect birds as well as pigs and other mammals, and are responsible for most seasonal influenza epidemics. Influenza A viruses also cause influenza pandemics. Influenza A viruses are negatively stranded RNA viruses surrounded by protein coats. During infection

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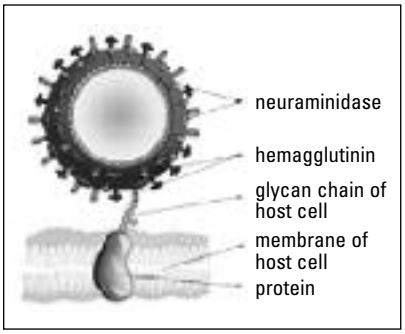

Figure. Influenza A virus infects a host cell.

Source: US National Institute of General Medical Sciences.

(**Figure**), a protein on the viral surface, hemagglutinin (H), attaches the virus to epithelial receptors in the respiratory tract. Viral RNA then replicates in the host cell nucleus, and another surface protein, neraminidase (N), allows the newly formed viral particles to be released from the host cell.[2]

Type A influenza viruses are further subtyped by their surface proteins—16 distinct hemagglutinins (H) and 9 distinct neuraminidases (N) are known, the combination of which is used to designate the subtype (e.g., H1N1, H3N2). All 16 hemagglutinins and 9 neuraminidases can infect birds, causing avian influenza, but only a subset (H1, H2, and H3; N1 and N2) typically circulate among humans.[2]

Influenza A viruses lack a mechanism for correcting mistakes that occur during viral replication, which can result in changes to the surface proteins. The continuous and relatively small changes that occur, known as "antigenic drift," produce new strains of virus within the same virus subtype. Since influenza vaccines induce antibodies to surface viral proteins, influenza vaccines change yearly to reflect the change in circulating strains. More substantial antigenic changes, known as "antigenic shift," occur more rarely and result in new subtypes by switching the combination of hemagglutinins and neuraminidases (e.g., H1N1 shifts to H2N2). There are a number of possible mechanisms for antigenic shift, including the reassortment of human influenza viruses with avian or swine viruses, or significant point mutations of avian or swine viruses.[2]

Past pandemics

Influenza pandemics are global outbreaks of influenza that occur with the appearance of a new influenza A subtype, or re-emergence of a subtype that has not been in circulation for many years. If a new subtype has either never circulated among humans, or has not done so for some time, the entire population is naive and susceptible to infection. In order for a new subtype to result in a pandemic, it must also cause significant human illness and be easily transmissible from person to person.

Although no expert can predict when the next pandemic will occur or how severe it will be, we can attempt to estimate overall impact using knowledge of previous pandemics.

The first clearly documented human influenza pandemic was described in 1580, and historians have since documented 31 influenza pandemics in total—suggesting that the appearance of new influenza A subtypes that can circulate among humans is inevitable. Most of our current understanding of influenza pandemics has been derived from the three pandemics that occurred in the 20th century: the 1918–19 "Spanish flu," the 1957 "Asian flu," and the 1968 "Hong Kong flu." The 1918–19 pandemic was due to an H1N1 virus, and caused as many as 50 million deaths worldwide during three distinct waves of illness over a 2-year period. The case fatality rate (i.e., the proportion of those infected who died) has been estimated to have been less than 5%.[3] No antivirals or antibiotics were available at the time to treat primary or secondary pneumonia. The 1918–19 pandemic was unique not only in its virulence but in its high mortality rate among young adults. The 1957 pandemic, caused by an H2N2 virus, was milder, resulting in an estimated 1 million deaths worldwide and a case fatality rate of less than 0.1%.[4] The mortality rate was highest among traditional high-risk groups for influenza (e.g., the elderly). The 1968 pandemic, caused by an H3N2 virus, was milder still.[2]

After each pandemic of the 20th century, the new subtypes of influenza A continued to circulate, causing predictable annual seasonal influenza outbreaks. The H1N1 subtype remained in circulation from 1918 until 1957, when it was replaced by the H2N2 sub-

Estimating the impact of pandemic influenza on the BC health care system

During an influenza pandemic, the BC health care system will not continue to function in the usual fashion. Health care deliverers, planners, and managers are being encouraged to use scenarios and planning assumptions to develop mitigating strategies that address issues such as determining if elective surgeries will continue at the usual rates, and ensuring there are triage protocols for clinical care resources developed with the aid and assistance of bioethicists. To reduce the burden on primary care, health authorities will also provide self-care information to the public during a pandemic, including details on how to stay healthy, what symptoms to look for, how to take care of your own illness, and when to seek medical care.

The BC Ministry of Health has used the pandemic parameters included in FluSurge (the pandemic estimation tool developed by the US Centers for Disease Control and Prevention)[5] to predict the demand on the BC health care system. The basic assumptions from this model are:

- There will be a 35% clinical attack rate.
- Half of those infected will seek ambulatory care.
- 1.3% of the 35% infected will require hospitalization.

Epidemics in populous areas will have sharper peaks than those in less populous areas. The peak period of the epidemic curves will likely be between 3 and 5 weeks in duration. In the absence of mitigating antiviral strategy or a pandemic vaccine, both of which are being planned for at the provincial and national levels, the following scenarios could be anticipated during a peak epidemic week:

- A 40% increase in GP visits over the average of 377 651 weekly fee-for-service physician visits.
- A 40% increase in emergency room visits over the average of 33 644 weekly visits.
- A 50% increase in weekly hospital admissions over the baseline of 6755 weekly admissions.
- A 250% increase in demand for ICU beds.
- A 50% increase in demand for respirators.

One model[6] estimates that judicious use of antiviral drugs to treat 20% to 25% of the population within 48 hours of influenza onset could lead to a 50% to 77% reduction in hospital demand; other studies suggest that such a strategy could reduce serious respiratory sequelae and antibiotic demand by 50%. Canada is presently acquiring stockpiles of antivirals to treat 17.5% of the population (assuming that not all of those who become ill will seek treatment in a timely way).

type. H2N2 remained in circulation until 1968, when the H3N2 subtype appeared. H3N2 has remained in circulation since 1968, causing most seasonal influenza outbreaks. In 1977, the H1N1 subtype reappeared, causing the "Russian flu," which is sometimes referred to as a "benign pandemic" because it primarily affected those under 20 years of age who had been born after 1957, when H1N1 was last in broad circulation, and for this reason did not produce significantly increased morbidity or mortality. H1N1 has remained in circulation along with H3N2 since 1977, and each year the trivalent influenza vaccine contains strains of influenza A/H3N2, influenza A/H1N1, and an influenza B strain.

Although pandemic subtypes continue to circulate for years after their initial appearance, morbidity and mortality decrease, presumably because of increased antibody levels in the population, decreased inherent virulence of the virus, or both. Infection with a particular influenza A subtype confers some protection against future infection with the same subtype. This also explains why young infants experience greater morbidity from influenza infection than older children and adults—this is their first exposure to the virus.

Although no expert can predict when the next pandemic will occur or how severe it will be, we can attempt to estimate overall impact using our knowledge of previous pandemics. One estimate of the potential impact of a pandemic on morbidity, mortality, and health care demand is described in the accompanying box,[5,6] "Estimating the impact of pandemic influenza on the BC health care system." This is a rough estimate, based on the 1957 and 1968 pandemics, and should therefore be interpreted only as an indication of the order of magnitude of morbidity and mortality we could see in a pandemic of the severity of those two pandemics. Estimates like this can better inform our pandemic planning.

Avian influenza

Recent research has increased our understanding of how pandemic influenza subtypes arise, and the importance of avian or swine influenza subtypes as potential sources of human pandemics. Avian influenza outbreaks are not new, and have always been of concern to the poultry industry because of their economic impact. Since the 1968 pandemic, there have been numerous reports of small numbers of people infected with swine or avian strains, but none of these instances have led to a pandemic. A classic example is the "swine flu" outbreak in Fort Dix, New Jersey, in 1976, which resulted in the rapid development of the swine flu vaccine and immunization of 40 million people. There is no evidence this virus ever spread beyond one military camp and this episode taught us that the emergence of a new subtype may be necessary, but is not necessarily sufficient, to cause a pan-

demic. In fact, many new subtypes, usually of swine or avian origin, have appeared since 1976, none of which precipitated a human pandemic.

The first known human infections caused by the H5N1 avian influenza occurred in Hong Kong in 1997. After an outbreak occurred in Hong Kong poultry, 18 human cases were identified and 6 people died, resulting in the culling of 1.5 million birds (practically the entire poultry stock in the territory at the time). Although all the human cases had contact with live poultry and there was no evidence of human transmission, there was concern because of the severity of human illness produced by this virus: most previous reports of human cases of avian influenza had resulted in mild illness. In October 2003, an H5N1 outbreak among poultry was reported in Asia and has since spread through numerous countries in Asia, the Middle East, Europe, and Africa. The scope of this avian outbreak, which may create greater opportunities for viral mutations or mixing to occur, has led many experts to believe that H5N1 may be a prime candidate for the next pandemic. This has resulted in heightened surveillance worldwide for avian and human cases of H5N1. As of 11 April 2007, the World Health Organization had confirmed 291 human cases and 172 deaths due to H5N1 as reported in 12 countries over a 4-year period.[7]

Whether H5N1 has the potential to become easily transmissible from person to person is not known. Almost all reported and confirmed cases to date have had direct contact with ill poultry. Reports of limited human-to-human transmission in Vietnam, Thailand, and Indonesia are certainly of concern, but there is no evidence that subtypes other than H1, H2, and H3 have ever circulated in human populations.[8] A recent report in the publication *Nature* found that the H5N1 virus attaches to receptors and replicates in the lower, not the upper, respiratory tract.[8] This may explain why H5N1 does not easily spread from person to person by droplets produced when coughing or sneezing, and raises the possibility that this subtype may not possess the potential to circulate widely among humans. The probability of H5N1 mutating to become transmissible to humans cannot be predicted with certainty. Although it has spread among birds to an unprecedented degree (and has affected a few other animal species, such as tigers), and has had many opportunities to mutate or reassort with human influenza viruses, H5N1 has not precipitated a human pandemic in the more than 10 years since it was first identified.[6] While monitoring H5N1 for its pandemic potential is important, we must not imply that the risk from H5N1 is inevitable, imminent, or as yet well understood.

Table. Responding to an influenza pandemic.

Pandemic phases	Overarching public health goals
Interpandemic period **Phase 1.** No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, risk of human infection or disease is considered to be low.	Strengthen influenza pandemic preparedness at the global, national, provincial, and regional levels.
Phase 2. No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease.	Minimize the risk of transmission to humans, and report such transmission rapidly if it occurs.
Pandemic alert period **Phase 3.** Human infection(s) with a new subtype, but no human-to-human spread, or at most rare instances of spread to a close contact.	Ensure rapid characterization of the new virus subtype and early detection, notification, and response to additional cases.
Phase 4. Small cluster(s) with limited human-to-human transmission but spread is highly localized, suggesting the virus is not well adapted to humans.	Contain the new virus within limited foci or delay spread to gain time to implement preparedness measures, including vaccine development.
Phase 5. Larger cluster(s), but human-to-human spread still localized, suggesting that the virus is becoming increasingly better adapted to humans, but may not yet be fully transmissible (substantial pandemic risk).	Maximize efforts to contain or delay spread, to possibly avert a pandemic, and to gain time to implement pandemic response measures.
Pandemic period **Phase 6.** Pandemic phase: increased and sustained transmission in general population.	Minimize impact of the pandemic.
Postpandemic period Return to interpandemic period characteristics.	Strengthen influenza pandemic preparedness at the global, national, and regional levels.

Source: Adapted from WHO global influenza preparedness plan.[9]

Pandemic phases

The World Health Organization's summary of pandemic phases (**Table**) describes the evolution of pandemics from the emergence of a novel virus

through to a worldwide epidemic.[9] The construct of pandemic phases should not, however, be interpreted as a sequential timeline. The progression from one phase to the next has never been observed empirically, and the probability of proceeding from one phase to the next cannot be predicted.

By planning together, public health and community physicians can create links that will not only prepare us for a pandemic, but allow us to deliver better care to our patients at all times.

Currently, we are in the pandemic alert period, Phase 3, because even though the novel H5N1 influenza virus can infect humans and cause severe illness, it does not transmit easily from person to person.

In the past, many undetected novel influenza viruses may have emerged and caused isolated cases of severe illness among humans. We must not assume that a heightened level of surveillance and greater understanding mean a heightened level of risk. In the last three pandemics, the outbreak only became recognized during Phase 6, the pandemic period.

Summary

Planning for pandemic influenza is necessary and worthwhile. Since we understand the epidemiology and clinical manifestations of influenza, we can plan according to expected parameters, such as incubation period and modes of transmission. We may need to change our approach as we learn specifics of the next pandemic strain, but with integrated surveillance systems, the availability of antimicrobials and antivirals, and appropriate and consistent infection control practices, health care providers can limit the impact of the pandemic until a vaccine can be produced and delivered. Since a pandemic vaccine will be the only definitive intervention to effectively control the pandemic, we need to support influenza vaccine research now. New influenza vaccine strategies may shorten preparation time, improve the immune response, or produce universal influenza virus vaccines.[10] By planning together, public health and community physicians can create links that will not only prepare us for a pandemic, but allow us to deliver better care to our patients at all times.

Competing interests

Dr Daly has received honoraria for educational sessions on unrelated topics from pharmaceutical companies that manufacture vaccines mentioned in these articles. Dr Gustafson has received fees for speaking from Merck Frosst Canada and a grant-in-aid contribution toward research from GlaxoSmithKline.

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