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INFLUENZA PANDEMIC

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INTRODUCTION

The recent emergence of "avian flu" in Asian countries, and its limited spread to humans, has initiated widespread speculation that this will spark an influenza (flu) pandemic among humans. A pandemic describes an outbreak of a specific illness, in epidemic proportions and in multiple areas covering a vast geographical area. This paper will examine the origins of the flu and describe some flu pandemics that have afflicted humankind in the past. It will also describe the current avian flu crisis and how this may, or may not, relate to a potential human pandemic. Finally, it will explore interventions for combating the flu as well as the plans, both Canadian and international, for pandemic preparedness.

THE FLU AND THE VIRUSES THAT CAUSE IT

Influenza, or flu, is caused by viruses that infect the respiratory and/or the gastrointestinal tract of mammals and birds. Compared with most other viral respiratory infections, such as the common cold, influenza infection often causes a more severe illness. Typical symptoms of the flu include fever, cough, sore throat, runny or stuffy nose, headache, muscle aches, and often extreme fatigue. Although nausea, vomiting, and diarrhea sometimes accompany influenza infection, especially in children, gastrointestinal symptoms are rarely prominent. The term "stomach flu" is a misnomer that is sometimes used to describe gastrointestinal illnesses caused by other micro-organisms.

Viruses are unique organisms that cannot be clearly categorized as either living or non-living. They infect another organism by attaching to it and injecting their own genetic material into the host's cell. The host's replicating machinery is then "hijacked" to produce multiple copies of the different viral components, which are repackaged as intact viruses that then leave the cell and go on to infect more host cells.

The influenza virus contains RNA (ribonucleic acid) as its genetic material (instead of the more common deoxyribonucleic acid, or DNA, found in all other forms of life), and can be divided into three main types (A, B, and C) based on differences within two of its major internal proteins. Type A influenza virus is found in a variety of birds and mammals and can mutate easily, while type B is confined to humans. Influenza virus types A and B are both associated with significant illness and death in humans. Type C does not appear to affect humans.

Influenza virus type A is further divided into subtypes based on membrane proteins (proteins on the virus's external surface). Surface proteins are significant, since they are the principal targets of the immune response. In type A, subtypes are distinguished by differences in the surface proteins hemagglutinin (HA) and neuraminidase (NA). HA is associated with the virus's affinity to bind to a host cell via a receptor in order to infect it, while NA is involved in the virus's escape back out of the host cell after infection. The notation H*x*N*y* is used to refer to the various subtypes. Subtypes are further divided into strains. While there are 15 known HA subtypes and 9 NA subtypes of influenza virus type A, only two subtypes are currently circulating in humans: H1N1 and H3N2. Type B influenza virus has not been found to include different subtypes.

THE INFLUENZA VIRUS ELUDES OUR IMMUNE SYSTEM

Based on descriptions of past epidemics and pandemics suggestive of influenza, humans have probably coexisted with flu viruses for at least 400 years. Viruses have been successful and continue to thrive because they can exist within some animals without causing illness and because they are often able to escape destruction by an animal's immune system. When exposed to a virus, our immune response includes the production of antibodies that help to remove the virus from our bodies. In order for a virus to avoid being destroyed by antibodies, it must be able to keep a step ahead of the host's immune response. This is done through antigenic variation, meaning that spontaneous genetic mutations in the virus bring about variations in the cell surface proteins mentioned above that provoke the immune response. This variation is brought about in two ways: antigenic drift or antigenic shift.

Antigenic drift refers to small mutations in the genes for NA and HA that may or may not bring about a structural change in the protein. This is a slow and inefficient means to elude host immunity.

Antigenic shift, on the other hand, describes major antigenic change whereby a virus with a new protein is introduced into the human population. This can happen in two different ways. First, it may occur when a new virus results from reassortment, or mixing, of animal and human influenza viruses. For example, this could occur when a person who is already infected with a human flu virus is also infected with an avian virus. Within the human host, the viruses mix (reassort) and a new virus containing a combination of human and avian genes is produced. Second, antigenic shift may occur when an animal flu virus evolves over time and at some point is introduced to humans. For example, a non-pathogenic (not producing sickness) avian virus could evolve slowly – over years or decades – in the bird population, totally isolated from any human exposure. At some point it could be introduced to humans and cause illness. This second form of antigenic shift appears to be much rarer than the first. Both types of antigenic shift may also occur through an intermediate host, most often pigs. Antigenic shift occurs only among influenza A viruses, and poses a greater risk for human epidemics and pandemics than does antigenic drift. This is because drift does not necessarily bring about a significant change in the viral protein structure, and therefore the host's existing antibodies may still be effective.

INFLUENZA A VIRUS

As indicated earlier, type A flu virus is found in birds and mammals, including humans. Birds, however, specifically shorebirds and waterfowl, appear to be the natural reservoir for influenza A virus. Birds infected with the viruses generally suffer no illness, although infrequently there may be flu-like symptoms. Infected birds excrete high levels of virus, and if excreted into bodies of water the virus may survive for several weeks. Other susceptible avian species, such as chickens or turkeys, may then become infected through contact with or drinking the water. A seemingly harmless virus in waterfowl such as ducks and geese may cause significant illness, or death, in another avian species such as chickens. The current avian flu type A H5N1 is harmless for ducks but is very pathogenic, or deadly, for chickens.

Reports of humans becoming infected with avian flu virus are rare, and such cross-species infections have proven very difficult to achieve under experimental conditions. This suggests that avian flu viruses are very limited in their ability to thrive in a human host. It has been the general consensus that an avian virus would have to acquire one or more genes from a human influenza A virus before it could effectively cross the species barrier. Because pigs can be infected with both avian and human influenza A viruses, it has been proposed that pigs may be the intermediate host required for the genetic reassortment needed before the virus can cross the species barrier and infect humans.

PANDEMICS OF THE 20TH CENTURY

As discussed above, the influenza virus outpaces the human immune response through antigenic shift. Three antigenic shifts in the 20th century produced pandemics, all of which have been described as being caused by type A viruses of avian origin. It has been estimated that there have been as many as 20 flu pandemics in the past 250 years.

A. The 1918 "Spanish Flu"

By the fall of 1918, Europeans had begun to refer to this outbreak as the "Spanish flu" probably because Spain, as a neutral country in World War I, had not imposed censorship of news about the disease that was sweeping many combatant countries. The most deadly of the recent pandemics, this flu killed between 20 and 40 million people worldwide, 30,000-50,000 in Canada alone.

There has been considerable controversy as to the geographic as well as viral origins of this pandemic. The virus that caused it was an H1N1 subtype. Biological samples kept from soldiers who died in the pandemic, as well as samples taken from bodies buried in the permafrost in Alaska of victims who were known to have died from the pandemic, have been recently analyzed. All the genes within the responsible virus appear to be of avian origin. That is, there was no reassortment with human flu genes. This finding indicates that the H1N1 virus that produced the 1918 pandemic arose from the second, less common, type of antigenic shift described above: an animal virus that is transmitted to the human species, or another animal species, without any mixing with other viruses. Investigators believe that the virus was an avian

strain that had evolved in isolation from the typical wild waterfowl influenza gene pool for some time. It then emerged into circulation among humans via an as yet unknown animal host, most probably swine. It has also been shown that the HA protein of H1N1 had a three-dimensional shape that helped it bind tightly to the human receptor and infect cells.

B. The 1957 Asian Flu

As mentioned earlier, only two subtypes of influenza type A are currently circulating in the human population, H1N1 and H3N2. While the 1957 pandemic was caused by H2N2, it has not been isolated from any outbreaks since and is not believed to be in circulation any longer.

The outbreak first erupted in southern China in February 1957, and had spread worldwide by November of that year. The virus was first isolated in Japan in May 1957 and was found to possess distinctly different HA and NA antigens than the previously recognized H1N1 viruses. Almost 70,000 people died and mortality was especially high among children, at greater than 50%.

C. The 1968 Hong Kong Flu

The virus responsible for the most recent flu pandemic was isolated in Hong Kong in July 1968. Again, children were especially affected, with mortality rates as high as 40%. Genetic studies have established that the viruses responsible for the pandemics of 1957 and 1968 were both the products of antigenic shift through reassortment. H2N2, of the 1957 pandemic, is believed to have arisen through reassortment between an avian influenza A virus and a circulating human influenza A (H1N1) virus. The virus responsible for the 1968 pandemic was found to have the same NA as the previously circulating H2N2, but a new HA. The 1968 influenza type A H3N2 virus was a reassortment of a new avian influenza A and the circulating H2N2.

THE AVIAN FLU

The current avian flu that is being monitored very closely in Asia is type A subtype H5N1, which, as stated earlier, is not one of the subtypes known to be circulating in the human population.

In May 1997, H5N1 was first isolated from a three-year-old child in Hong Kong. Genetically similar influenza A H5N1 had been isolated from sick chickens on nearby farms in the same year. The child, therefore, was suspected to have become infected with a purely avian strain through infected chickens. Although there was no direct link between the sick child and these farms, the child's school kept chicks and ducklings which may have been obtained from neighbouring farms. Within six months, 17 more cases were identified and 6 of the 18 people died from the infection. Studies revealed that, up to this time, all infections were poultry-to-human and not human-to-human. Closure of live bird markets and mass extermination of poultry and fowl in Hong Kong in December 1997 seemed to be successful in stopping the outbreak.

The strain did not re-emerge until 2003, when two family members in Hong Kong became infected and one died. It has not been determined how or where these infections originated. In 2004, 44 people became infected with H5N1, of whom 32 died. Most of these people had close contact with poultry and there has been little evidence of efficient person-to-person transmission. As of the beginning of February 2005, a total of 52 people had contracted H5N1 and 42 people had died.

The H5N1 virus subtype represents an increasing global concern for public health. In 2003, the H5N1 virus subtype underwent certain changes that produced a new strain that may have increased pathogenicity. The so-called "Z strain" has now spread to nine Asian countries in various animal species. This strain is characterized by pathogenicity in a broader range of animals than normally seen and resistance to older antiviral drugs. While transmission of this virus from birds to humans has been documented for most of the cases, human-to-human transmission has been demonstrated to have probably occurred in two cases. Therefore, because of the documented increase in the virus's pathogenicity in animals and humans, as well as its ability to be transmitted human-to-human, there is particular concern that H5N1 will be responsible for the next flu pandemic.

Whether the current avian H5N1 will spark the next pandemic depends on several factors, including:

- a new influenza A virus, i.e., a variant of the H5N1 subtype, arising from a major genetic change, such as an antigenic shift;
- a virus that is transmitted efficiently from person to person;
- a virus with the capacity to cause serious illness and death; and
- a susceptible population with little or no immunity.

The first of these conditions could include a reassortment of the current avian virus with a human virus, which appears not to have happened yet. The persistence of this virus in Asia, however, leads many experts to conclude that this reassortment will eventually happen.

INTERVENTIONS

There is a certain level of optimism that future pandemics, while inevitable, may be controllable. The World Health Organization and most developed countries have surveillance programs that will allow early detection of outbreaks and possibly the prevention of a pandemic. In the event of a pandemic, however, there are certain interventions that can be taken to help reduce the spread or severity of the outbreak.

The first of these interventions is isolation. This measure was used very successfully during the outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003. An efficient surveillance and reporting system permits effective identification of infected individuals, who can be quarantined to prevent further spread. This is a critical step in reducing the spread of any communicable disease.

Medical interventions that are now available include vaccines and antiviral drugs. A vaccine for the flu was first tested in 1935 and has been recommended for general use since the 1960s. Because the virus evolves so rapidly, a new vaccine must be designed each year. The current vaccine used in most countries worldwide contains three inactivated virus types: a type B influenza, and the current circulating strain of each influenza type A H1N1 and H3N2. Although the type A strain that is circulating is different from those used in the vaccine, it is believed that the vaccine stills offers some protection. However, because vaccines take at least three months to produce, they are of limited use at the outset of an outbreak. In the event that a

new and virulent strain appeared in humans, the infection could spread significantly before a vaccine could be made available.

The other intervention that can be employed in the face of a flu outbreak is antiviral medication. Antivirals will likely be used as the first medical intervention in the event of a pandemic, given the time required to prepare a new vaccine. Currently, four antivirals are approved for use in fighting the flu. Two drugs are categorized as M2 inhibitors; these are amantadine and rimantadine. These drugs interfere with a viral protein called M2 and prevent activation of the viral genetic material. M2 inhibitors are associated with significant side effects on the gastrointestinal and central nervous systems. The flu virus also seems to quickly become resistant to this drug.

The second class of antivirals are NA inhibitors; these are zanamivir and oseltamivir. These drugs inhibit the action of NA and prevent the new virus from leaving an infected cell. In the Netherlands in 2003, an outbreak of an avian influenza type A H7N7 was effectively controlled with the use of oseltamivir. This antiviral drug has also been shown to be effective against H5N1. NA inhibitors have less severe side effects than the M2 inhibitors. Development of new anti-influenza drugs is an active area of research.

THE CANADIAN PANDEMIC INFLUENZA PLAN

In February 2004, Canada's federal/provincial/territorial Pandemic Influenza Committee issued the most recent Canadian Pandemic Influenza Plan. The mandate of the Committee, which first convened in March 2002, is to provide advice, expertise and recommendations, liaison and other activities associated with all phases of a flu pandemic. The plan is meant as an outline for planning, preparedness and response to pandemic influenza by the different levels of government.

Canada has had a pandemic influenza plan since 1988. It is continually updated based on research, experience within Canada and experiences in other countries with disease outbreaks. The plan is based on basic principles of public health and emergency response. Its goals are to minimize illness and death while also minimizing the social disruption. These aims can be realized only if the different levels of government are able to coordinate their activities.

The plan's February 2004 update employs the "Pandemic Phases" used by the World Health Organization and specifies the response component, actions required and the levels

of government involved for each phase. The preparedness phase is Phase 0, which has three levels of action: 1. A novel virus isolated from a human; 2. Two or more humans infected with the novel virus; and 3. Human-to-human transmission confirmed. Most of the actions outlined in Phase 0 assume that such events will not occur in Canada; however, this approach will be relevant should a novel influenza virus erupt in Canada. Phase 1 describes activities required when outbreaks are confirmed in multiple geographic locations outside of Canada, confirming a pandemic. Phase 2 refers to outbreaks in multiple geographic areas within Canada. Phase 3 deals with the end of the first wave, while Phase 4 describes the second and subsequent waves of infection, should they occur. Phase 5 describes the activities for a post-pandemic or recovery phase.

For each phase the plan describes surveillance, vaccine programs, antivirals, health services, emergency services, public health measures and communications. The plan describes in detail the actions required for each of these components and specifies, for each of those actions, which levels of government have a role.

National surveillance is carried out by the Public Health Agency of Canada (PHAC) under "FluWatch." The Viral Respiratory Diseases Section, within the Immunization and Respiratory Infections Division of the PHAC's Centre for Infectious Disease Prevention and Control (CIDPC), produces regular FluWatch reports, summarizing influenza surveillance activities in Canada. Reports are produced weekly during the influenza season (October to May) and biweekly during the off season (June to September). Influenza surveillance is a collaborative effort between provincial and territorial ministries of health, participating laboratories, The College of Family Physicians of Canada, sentinel physicians, and the CIDPC.

The PHAC maintains contact with the World Health Organization (WHO) and is kept informed of any possible global outbreaks. Additionally, the PHAC maintains the Global Public Health Intelligence Network (GPHIN), which is a secure, Internet-based early warning system that gathers preliminary reports of public health significance by monitoring global media sources on a real-time, 24/7 basis. Notifications about events that may have serious public health consequences are immediately forwarded to users. This system is not limited to influenza but can include other infectious diseases, contaminated food and water, bioterrorism and exposure to chemical and radio-nuclear agents, and natural disasters.

On 4 February 2005, the federal Minister of Health announced that the government would be securing a stockpile of the antiviral drug oseltamivir sufficient to medicate nearly 1 million Canadians. In the event of a pandemic, the government has already arranged for a drug manufacturer to produce sufficient vaccine for all Canadians.

WORLD HEALTH ORGANIZATION'S INFLUENZA PANDEMIC PREPAREDNESS AND RESPONSE

The WHO Global Influenza Surveillance Network is used to enable the WHO to recommend twice annually the content of the influenza vaccine for the subsequent influenza season. It also serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential. Its activities have contributed greatly to the understanding of influenza epidemiology. The network was established in 1952, in response to a WHO Expert Committee's recommendation that an international network of laboratories be created that would enable the WHO to advise Member States as to what influenza control measures are useful, useless or harmful.

The components of the WHO Global Influenza Surveillance Network are:

- National Influenza Centres (NICs), which sample patients with influenza-like illness;
- WHO Collaborating Centres, which perform antigenic and genetic analyses of the samples submitted by NICs; and
- the WHO itself, which coordinates all information.

Currently, 112 institutions from 83 countries, including Canada, are recognized by the WHO as National Influenza Centres.

The World Health Organization has recognized that a successful vaccination program is the best way to limit the impact of future flu pandemics. In November 2004, the WHO held an informal meeting with influenza vaccine manufacturers, national licensing agencies and government representatives on influenza pandemic vaccines. The summary report that followed, *Vaccines for pandemic influenza,* outlines measures that should be taken in order to ensure an adequate supply of effective vaccine. Some of the aspects that participants agreed on were that: clinical trials to establish vaccine formulation should be coordinated internationally to facilitate the exchange of information; strategies for stretching limited supplies of vaccine (termed antigen-sparing strategies) must be explored; domestic licensing and international marketing of vaccines must be facilitated; and the establishment of national and international stockpiling must be a priority.

On 20 January 2005, the WHO issued a report entitled *Influenza pandemic preparedness and response*. The report emphasized the importance of the WHO's role in maintaining worldwide surveillance and disseminating information regarding flu outbreaks. It also reiterated the need for a coordinated response with respect to vaccine production and the importance of stockpiling antivirals and vaccines.

CONCLUSION

The occurrence of another flu pandemic is inevitable, and most experts expect that it will happen sooner rather than later. The avian influenza type A H5N1 is considered a likely candidate for the next pandemic. This prediction presents a unique opportunity for the world community. For the first time in history, humankind is in a position to be able to prepare a vaccine that may enable a rapid response to a global outbreak. Given the virulence of this strain of influenza (as high as 75% mortality), it is crucial that Canada remain vigilant in its surveillance and response efforts.

REFERENCES

Cox, N. J., and K. Subbarao. "Global Epidemiology of Influenza: Past and Present." *Annual Review of Medicine,* Vol. 51, 2000, pp. 407-421.

Earn, David J. D., Jonathan Dushoff, and Simon A. Levin. "Ecology and evolution of the flu." *Trends in Ecology and Evolution,* Vol. 17, 2002, pp. 334-340.

Laver, Graeme, and Elspeth Garman. "The Origin and Control of Pandemic Influenza." *Science,* Vol. 293, 2001, pp. 1776-1777.

Monto, Arnold S. "The Threat of an Avian Influenza Pandemic." *New England Journal of Medicine,* Vol. 352, 2005, pp. 352-354.

Taubenberger, Jeffrey K., *et al.* "Capturing a Killer Flu Virus." *Scientific American,* Vol. 292, 2005, pp. 62-71.

Ungchusak, Kumnuan, *et al.* "Probable Person-to-Person Transmission of Avian Influenza A (H5N1)." *New England Journal of Medicine,* Vol. 392, 2005, pp. 333-340.

Information regarding the World Health Organization is available on its Web site at: www.who.int.

Information regarding the Public Health Agency of Canada is available on its Web site at: www.phac-aspc.gc.ca.