The Next Influenza Pandemic: Lessons from Hong Kong, 1997

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The 1997 Hong Kong outbreak of an avian influenzalike virus, with 18 proven human cases, many severe or fatal, highlighted the challenges of novel influenza viruses. Lessons from this episode can improve international and national planning for influenza pandemics in seven areas: expanded international commitment to first responses to pandemic threats; surveillance for influenza in key densely populated areas with large live-animal markets; new, economical diagnostic tests not based on eggs; contingency procedures for diagnostic work with highly pathogenic viruses where biocontainment laboratories do not exist; ability of health facilities in developing nations to communicate electronically, nationally and internationally; licenses for new vaccine production methods; and improved equity in supply of pharmaceutical products, as well as availability of basic health services, during a global influenza crisis. The Hong Kong epidemic also underscores the need for national committees and country-specific pandemic plans.

Influenza pandemics are typically characterized by the rapid spread of a novel type of influenza virus to all areas of the world, resulting in an unusually high number of illnesses and deaths for approximately 2 to 3 years. Such pandemics occurred in 1918, 1957, and 1968 (Table); in the most severe pandemic (1918-20), at least 20 million people died, most working-age adults (10-12). Most deaths occurred in developing nations—more than 10 million people died in India alone (M. Rammana, pers. comm.). Pregnant women were also severely affected, particularly those from lower socioeconomic groups (13,14). The age distribution of those who died differed from that in later pandemics or epidemics, when deaths were higher in the elderly and lower in other age groups, except possibly in very young children.

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Novel Influenza Viruses without Pandemics

In addition to true pandemics, false alarms—emergences of a novel strain with few cases and little human transmissibility (Table)—have occurred. Several involved "swine influenza viruses" (4-6) antigenically related to viruses circulating in some pig populations and linked to viruses of the 1918 pandemic (see below). These unusual infections may be more common than reported, as laboratory diagnosis for influenza is rarely undertaken in the absence of unusual illness or association with an outbreak.

Origin of Pandemic Viruses

Before influenza virus could be propagated in a laboratory, retrospective measurement of antibodies to the influenza virus' major surface antigen (hemagglutinin) in persons of different ages was used to identify viruses causing pandemics. Additional use of antibody tests to the second surface antigen (neuraminidase) confirmed earlier ideas that H1N1 subtype viruses resembling classic swine influenza caused the 1918 pandemic (15).

Table. Influenza landmarks in humans this century

Year	Colloquial Name (Subtype)	Source	Impact
Pandemics			
1918 (1)	Spanish flu (H1N1 viruses like swine flu)	Possible emergence from swine or an avian host of a mutated H1N1 virus	Pandemic with >20 million deaths globally
1957 (2)	Asian flu (H2N2)	Possible mixed infection of an animal with human H1N1 and avian H2N2 virus strains in Asia	Pandemic, H1N1 virus disappeared
1968 (2)	Hong Kong flu (H3N2)	High probability of mixed infection of an animal with human H2N2 and avian H3Nx virus strains in Asia	Pandemic, H2N2 virus disappeared
1977 (3)	Russian flu (H1N1)	Source unknown, but virus is almost identical to human epidemic strains from 1950. Reappearance detected at almost the same time in China and Siberia	Benign pandemic, primarily involving persons born after the 1950s. H1N1 virus has cocirculated with H3N2 virus in humans since 1977
Incidents with limited spread			
1976 (4)	Swine flu (H1N1)	United States/New Jersey. Virus enzootic in U.S. swine herds since at least 1930	Localized outbreak in military training camp, with one death
1986 (5)	(H1N1)	The Netherlands. Swine virus derived from avian source	One adult with severe pneumonia
1988 (6)	Swine flu (H1N1)	United States/Wisconsin. Swine virus	Pregnant woman died after exposure to sick pig
1993 (7)	(H3N2)	The Netherlands. Swine reassortant between old human H3N2 (1973/75-like) and avian H1N1	Two children with mild disease. Fathers suspected to have transmitted the virus to the children after having been infected by pigs.
1995 (8)	(H7N7)	United Kingdom Duck virus	One adult with conjunctivitis
1997 (9)	Chicken flu (H5N1)	Hong Kong Poultry virus	18 confirmed human cases, 6 deaths

Molecular biologic analysis of viral nucleic acid supports the hypothesis that animals (particularly birds and pigs) may have been the source for (and possibly are a continuing reservoir of) the hemagglutinin and other genes found in viruses from the above pandemics (16). Some animal viruses containing these genes (e.g., H1, H2, H3) might infect humans directly and become adapted to the human host; alternately, through reassortment of the genes in different animal or human influenza viruses, the genetic information might reappear in an infectious human virus (17). The Hong Kong experience, however, showed that an animal virus with another HA subtype (H5) could directly infect humans and cause illness. The H5 virus, however, did not evolve into a form that is readily transmitted from person to person, and its potential for this kind of transmission remains unknown.

Reports in 1957, 1968, and 1977 indicated China and nearby areas as places where outbreaks of novel viruses often first occur (18). Close contact occurs in such regions between humans and animals (e.g., ducks, pigs) raised for food. Surveillance data show that because of the different seasonality of influenza in northern and southern China, human influenza infections normally occur every month of the year (19). Thus, many opportunities exist in China for viruses to cross-infect different animal species and humans, which may explain why it and nearby areas are the origin of many influenza pandemics.

Avian Influenza Virus in Humans in Hong Kong

In May 1997, a 3-year-old boy in Hong Kong contracted an influenzalike illness, was treated with salicylates, and died 12 days later with complications consistent with Reye syndrome. Laboratory diagnosis included the isolation in cell culture of a virus that was identified locally as influenza type A but could not be further characterized with reagents distributed for diagnosis of human influenza viruses. By August, further investigation with serologic and molecular techniques in the Netherlands

(9, 20, 21) and in the United States (22) had confirmed that the isolate was A/Hong Kong/156/97 (H5N1), which was very closely related to isolate A/Chicken/Hong Kong/258/97 (H5N1). The latter virus was considered representative of those responsible for severe outbreaks of disease on three rural chicken farms in Hong Kong during March 1997, during which several thousand chickens had died. Molecular analysis of the viral hemagglutinins showed a proteolytic cleavage site of the type found in highly pathogenic avian influenza viruses.

Because no further cases of human infection with H5 viruses were seen in Hong Kong during the summer, the case in May was considered an isolated incident, with little or no person-to-person spread. However, surveillance for influenza was increased, and local capability was established to test for H5 subtype among human patients.

As summarized on their Internet disease surveillance site, the Hong Kong Special Administrative Region Department of Health (http://www.info.gov.hk/dh/diseases/flu_1997.htm) detected new cases of human illness caused by H5 virus during November 1997. By late December, the total number of confirmed new cases had climbed to 17, of which 5 were fatal (one in a 13-year-old child and four in adults, 25, 34, 54, and 60 years of age). Including the fatal index case in May, the case-fatality rates were 18% in children and 57% in adults older than 17 years.

Investigation of the circumstances surrounding each case was undertaken by the local authorities with assistance from the World Health Organization Collaborating Centers in the United States and Japan. Except for one doubtful unconfirmed case, all illnesses or laboratory evidence of infection was in patients who had been near live chickens (e.g., in market places) in the days before onset of illness, which suggests direct transmission of virus from chicken to human rather than person-to-person spread. On December 28, 1997, veterinary authorities began to slaughter all (1.6 million) chickens present in wholesale facilities or vendors within Hong Kong, and importation of chickens from neighboring areas was stopped. Subsequently, no more human cases caused by avian influenza virus were detected. Because these cases occurred at the beginning of the usual influenza season in Hong Kong, public health officials were concerned that human strains might cocirculate with the avian influenza to generate human and avian reassortant viruses with capacity for efficient person-to-person spread.

Response to Emerging Influenza Pandemics. Lessons from Hong Kong

Pandemic planning has been proceeding in various countries and at WHO for several years (23). Now, 1 year after the Hong Kong episode ended, a period during which several countries have had severe local outbreaks or epidemics of interpandemic variant A/Sydney/5/97 (H3N2)-like viruses, lessons from Hong Kong could be incorporated in existing or new pandemic response plans.

Improve International Response

When the Hong Kong episode occurred, WHO had been developing formal guidelines for addressing pandemic situations. The draft guidelines were revised after the Hong Kong episode, taking into consideration two strategic steps especially important in the outbreak: risk assessment, which encompasses two components, data collection (investigating the circumstances of the initial infection and subsequent infections, and searching for further evidence of spread) and data evaluation (interpreting and communicating the significance of the threat based on the available data); and risk management, which is a process of continuously considering and updating alternative courses of action as new action is obtained, defining potential risks and benefits of each approach, and selecting the next step, or series of steps, recommended for appropriate authorities.

Having already established a Pandemic Task Force by 1997, WHO was able to initiate technical investigation and evaluation of the Hong Kong situation. Only a very few organizations, from the United States and Japan, rapidly committed staff to join local authorities in collecting information needed for risk assessment. The widespread local and international consequences of the situation in Hong Kong, including impact on commerce and travel, compounded the already large pressures on the investigating team to gather evidence about the risk for an epidemic or pandemic. Further pressure was exerted on the investigating team, WHO Task Force, and collaborating organizations because much work was urgently needed on a contingency basis to expand capabilities of international surveillance laboratories to detect H5 influenza viruses elsewhere and to support preliminary steps necessary for developing a vaccine against the Hong Kong virus.

Because influenza pandemic threats affect more than one country, facilitating multicountry studies could save critical time in the risk assessment process. Hence, increasing international involvement in both phases of risk assessment is desirable—both to expand resources for investigations and to ensure that all regions of the world, including developing nations, are represented during decision making. Advance commitments could be made to rapidly expand the network of academic, governmental, or other laboratories or disease-investigating organizations that can conduct field investigations and analyze potentially large numbers of isolates and other specimens. We suggest several ways for improving international response. First, the WHO Task Force could develop formal Terms of Reference for its own role and that of its investigating teams. Second, National Health Authorities of WHO member nations might then make these commitments: to invite WHO team(s) to carry out investigations of pandemic threats without delay, agree with the Terms of Reference for the task force and its investigating teams, and designate national organizations to assist investigating teams. Such advance agreements should facilitate the rapid deployment of investigating teams and the acceptance of their work by WHO member nations, regardless of what countries appear to be relevant sites for investigation of a pandemic threat or in what ways the pandemic threat is first identified or affects local interests. However, special questions will be raised regarding leadership, communications, and internal cooperation as more countries become involved, and these issues also should be addressed, if possible, in advance.

In setting Terms of Reference, data collection may be formally separated from risk evaluation and risk management. Such separation would allow technical experts to concentrate on organizing and conducting field and laboratory investigations without being distracted by having to evaluate the significance of findings or recommending responses to a pandemic threat (24). Furthermore, the willingness of some countries to receive WHO investigating teams may be enhanced if the Terms of Reference specify that data collected for the WHO Task Force will be evaluated by an independent advisory group composed of infectious disease and public health experts representing all WHO regions, including developing nations. Such a tiered approach would be consistent with ways many other public health policy decisions are made about epidemics.

Enhance Human and Veterinary Surveillance

Human influenza epidemics may be evaluated through death data (25-27), but weekly illness reports from sentinel primary-care practices, coupled with laboratory diagnosis, provides more timely detection of early isolates as well as epidemics (28,29). First detection of influenza outside the normal influenza season, however, may come from unsystematic sampling—epidemiologic investigations of reports of unusual outbreaks (e.g., most recently among tourists during summer in different parts of the United States [30], the events in Hong Kong in 1997).

The current WHO global influenza program, with the help of four collaborating centers (Atlanta, London, Melbourne, and Tokyo) and 110 national influenza centers, aims to centralize world data, study the epidemiology of the disease, and rapidly obtain new circulating strains to make timely recommendations about the composition of the next vaccine (31). However, many countries have only limited capabilities or resources to systematically search for and investigate unusual occurrences of influenza. The events in 1997 in Hong Kong show the need to expand routine surveillance efforts. Had the H5 virus isolated in May 1997 from a sporadic case not been identified in August, the reagents would not have been available locally to rapidly diagnose the additional human cases of H5 influenza in humans in November and December. Without such diagnoses, and the investigations which they stimulated, authorities might not have addressed the issue of chicken influenza as they did. Transmission of the H5 virus to humans could have continued into the normal influenza season in Hong Kong, possibly developing into a human-transmissible form.

Therefore, priority should be given to the establishment of regular surveillance and investigation of outbreaks of influenza in the most densely populated cities in key locations, particularly in tropical or other regions where urban markets provide opportunities for human-live animal contact (e.g., swine and poultry[and possibly caged birds kept as pets]). Communication and cooperative studies with veterinarians could monitor influenza outbreaks in locations where large numbers of animals are raised, exhibited, or held pending transport or sale, i.e., situations increasing the potential for virus spread. International collaboration with the WHO Collaborating Centers studying human influenza and the WHO Collaborating Center on influenza ecology in lower animals and birds (Memphis, USA) should be enhanced.

Develop Improved, Low-Cost, Laboratory Surveillance Techniques

For many years, influenza viruses have been isolated by injecting clinical samples into embryonated chicken eggs. Viruses have been detected by agglutination of erythrocytes and inhibited by using antisera provided through WHO, thus keeping costs relatively low and methods relatively simple. Laboratories in industrialized countries (including Hong Kong) have the facilities to use tissue culture for virus isolation. However, when the H5 viruses isolated in Hong Kong were injected into chicken eggs, they caused high numbers of deaths, thus making eggs less suitable as the sole host system for surveillance purposes. Thus, developing simple low-cost techniques (with reagents appropriate for the task of detecting circulation of animal influenza viruses) that can be used in places with limited resources needs to be a priority.

Choices must be made whether such tests should be based on isolation of infectious virus (which can immediately provide virus samples for biologic characterization and development of reagents or vaccines) or on antigenic or molecular methods (which may minimize laboratory capabilities needed). In making the choice of tests, it should be remembered that the reported isolation of an atypical virus by one or a very few laboratories may result from contamination of diagnostic specimens by viruses used for research, reagent production, or quality control; molecular techniques may be needed to confirm unrecognized cases of contamination with live viruses (32,33). It is unclear if diagnostic methods based on molecular methods will incur fewer risks from specimen contamination.

Increase Laboratory Safety Capabilities

The episode of H5, a potentially highly pathogenic virus for humans as well as for chickens and other avian species, also raised the issues of how to contain new viruses and protect laboratory workers and the environment. Although the 1918 pandemic strain was extremely pathogenic and was related to classic swine influenza virus, influenza diagnostic laboratories around the world do not use biologic containment procedures (biosafety level 3 or greater) to handle specimens. The Hong Kong experience shows that there can be no absolute certainty about the human pathogenicity or animal transmissibility of any influenza specimen.

Training of laboratory staff in national centers and local laboratories undertaking influenza surveillance, therefore, is needed to ensure that the best practices are routinely used to reduce infection or transmission risk. Contingency plans can be prepared to increase stringency of biological safety procedures, should an unusually pathogenic new influenza subtype again appear. Procedures would need to be appropriate for the technical facilities that actually exist in laboratories in different locations. Authorization to import and maintain supplies of an antiviral agent (e.g., rimantadine) could be organized in advance to protect laboratory workers and others at high risk. Procedures for authorized shipment of potentially hazardous strains to a reference center also can be planned in advance. Experience in 1997 also showed that the same needs may extend to the expanded network of laboratories likely to collaborate in investigations of new influenza viruses, including laboratories using live field strains of the virus for research, vaccine development, or reference material preparation.

Enhance Electronic Communications about Influenza

In 1997, the Hong Kong authorities set a new standard in communications about influenza by providing daily updates on a readily accessible Internet site. Information was also accessible on the FluNet WHO Internet site (http://

www.who.ch/flunet/). Further examples of electronic influenza information systems are the partial European system, which collects and disseminates data from seven countries (34); weekly information from the Centers for Disease Control and Prevention about influenza in the United States (http://www.cdc.gov/ncidod/diseases/flu/weekly.htm); and electronic (e)-mail by the Public Health Service in the United Kingdom, which disseminates up-to-date information on influenza occurrence there. However, these regional or national systems do not obviate the need for a single, universally accessible, global system that would enable national or local public health officials and laboratory workers to monitor influenza without receiving multiple e-mail messages or having to connect to different Internet sites that use varied formats, representations of data, and possibly languages. Such a system could have reduced uncertainty in late 1997 about whether the lack of reports of H5 viruses outside Hong Kong was due to lack of adequate searching for them or lack of their spread. This concern also is hard to address until it becomes possible to receive information electronically from, or provide technical guidance to, most local or national health centers in developing nations undertaking disease investigation and diagnosis.

Accordingly, development of a multifunctional electronic global influenza information exchange system is suggested. (Such a system could also be used to communicate about other important infectious diseases, so long as this does not complicate widespread accessibility for influenza information exchange.) This system would extend current capabilities beyond those of the existing WHO Flu-Net by ensuring the existence of resources (e.g., connection by wired or wireless communication systems) and system management procedures (e.g., authorization passwords and encryption) to allow simple daily access by all national influenza centers; extending access to local scientists and health officials in key cities within participating countries who, because of their surveillance or diagnostic capabilities, may have early information about possibly new influenza virus cases or outbreaks; enabling users to send and receive information rapidly within their own countries, as well as to or from WHO or the collaborating centers; and providing access also to key national and international scientists knowledgeable about occurrences of possible influenza outbreaks in animals. For scientists at a local level to benefit from international electronic information, translation into several major languages may be needed, on line if possible or at international or national Internet sites.

Among other benefits, information from an electronic information exchange system could enable local and national or international scientists to make cooperative decisions about diagnostic sampling and needed epidemiologic information, without the effort and expense of outside experts. Furthermore, operators of public electronic information sites, such as WHO, or a national authority, as was the case in Hong Kong, would be better able to fulfill their task if such a system were in place for them to collect and check information.

Enhance Vaccine Production Capabilities

Pathogenicity of the H5 virus for chickens and chicken eggs complicated the preparation of seed virus for potential production of vaccine, even for supplies for testing in humans; thus, a high-yielding production seed could not be easily adopted. Alternative strategies (e.g., attenuation of the virus by genetic manipulation, expression of the gene coding for the H5 virus into baculovirus-infected insect cells, or use of a nonpathogenic virus antigenically close to the currently isolated strain) were envisaged. However, even now, it is not clear that a practical way to mass-produce vaccine to the H5 Hong Kong virus exists or could be established in a short time, should a similar event occur. Thus, the rules for pandemic planning need revision, recognizing that reliance on existing licensed techniques for vaccine production could entail unacceptably long delays, should a highly pathogenic strain of avian influenza emerge and lead to a strain transmissible in humans (35).

Efforts begun in 1997 to find ways to mass-produce vaccine when the wild virus is highly lethal for eggs should be continued. These include producing vaccine with existing facilities (attenuating the effect of vaccine virus on eggs) and developing alternative techniques (e.g., cell culture grown virus, genetically engineered vaccines). Placing applications to license new methods on the fast track for review by regulatory authorities would be consistent with a basic tenet of pandemic preparedness: the greater the interpandemic production and use of influenza vaccine, the easier it will be to meet needs should a pandemic occur. Modifying vaccine-control procedures to decrease delays in releasing batches of vaccines in diverse countries with similar requirements in an emergency is also important. (This issue is already being discussed in Europe [J. Wood, pers. comm.].)

Improve Access to Vaccine or Antiviral Agents and Establish Support Systems

During the Hong Kong episode, a rapid local shortage of existing antiinfluenza drugs was observed, and rimantadine was imported. Had vaccines begun to be produced, no process existed for reaching agreements about access by different countries. Waiting until a pandemic strikes to determine access to prophylactic materials inevitably contributes to inequities in supply for countries lacking facilities to produce antiviral agents or vaccines or lacking resources to competitively purchase supplies at a time of scarcity. The issue of equity cannot be resolved by individual governments or manufacturers. Both vaccine and drug industry and international organizations need to discuss how to encourage fair distribution of scarce vaccines or other pharmaceutical drugs before a pandemic crisis arises.

Regardless of vaccine supply issues, vaccines and antiviral agents are unlikely to meet demand, even for industrialized countries able to purchase them. Assuming that people in all countries will be similarly susceptible to the next influenza pandemic virus and even though the elderly usually constitute a smaller percentage of the population in developing than in industrialized countries, during any future pandemic, the absolute number of those dying in the developing world will likely equal or exceed the number of those dying in industrialized countries, as in 1918. Other needs for responding medically must also be considered, including methods to ensure provision of basic nursing support and care when large numbers of people become ill over a few-week period in community after community. During the 1918 pandemic in the United States, for example, the Public Health Service called on the Red Cross to assume responsibility for mobilizing health workers and paying for them during the epidemic and supplying hospitals when local authorities could not (36). Efforts were mounted in many communities, even in remote areas with few facilities for health care. In India, efforts by individual communities without government directive were credited with saving many lives in 1918-19 (M. Rammana, pers. comm.).

Conclusions

One year after concerns were raised in Hong Kong about another influenza pandemic, are we really much further along in establishing the most effective early warning systems and developing the ability to deal with a true pandemic? WHO now has guidelines for responding to a pandemic (24). New helpful relationships, procedures, and scientific knowledge were undoubtedly established in 1997, particularly concerning international efforts for virus surveillance and vaccine production. However, both serious pandemic threats in recent years (1976, United States; 1997, Hong Kong) raised unpredictable new issues related to vaccine supply, which should not stand in the way of planning about the many predictable needs, which extend well beyond producing and using vaccines. For example, had the H5 viruses spread among the human population in Hong Kong (or any other country), national authorities would have rapidly needed to obtain numerous pharmaceutical products, to store and equitably distribute them, to manage demand for basic health-care services, and to maintain social and economic functions during a potential major health crisis (24). Because of the large variety of tasks, the formation of National Pandemic Planning Committees (NPPCs) has been suggested to develop the options for intervention strategies appropriate to each country (37).

Establishment of NPPCs will likely raise procedural matters, such as membership and chain of command. Unless these matters are resolved, valuable time will be lost. As seen in Hong Kong, a pandemic threat arises suddenly and rapidly becomes a public health concern. Yet very few countries have formally established NPPCs and influenza pandemic plans (a process requiring several years). Without increased urgency about this matter, the next pandemic will find most of the world unprepared.

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