Workshop 1: Surveillance Issues of Pandemic Influenza

The purpose of this workshop was to review the status of surveillance activities and to recommend new approaches necessary to detect and control pandemics. The specific questions that the panel addressed were as follows:

- *Is the current global surveillance network equipped to rapidly detect a new pandemic strain of influenza, to monitor the impact as the virus spreads, and to disseminate surveillance information in a timely manner?*
- *How can surveillance data be used to control a pandemic?*
- *What are the ways by which increased research efforts can improve virologic and disease surveillance?*

The panel agreed that adequate surveillance is critical for the prompt detection of influenza variants, including strains of pandemic potential. Both the detection of the viruses and the diseases they cause are components of this effort, which, by its very nature, must be international in scope. Surveillance questions were examined formally by the group, which included participants from France, Norway, Australia, Japan, Hong Kong, and the United States.

Current Global Surveillance Networks

Claude Hannoun, chair of the session, reported on two issues: the methods used over many years in France and now in other countries in Western Europe for surveillance and the absence of laboratories in certain parts of the world. In Europe, a system of sentinel physicians collects samples for virus isolation from practices covering large geographic areas. Specimens are transported to central laboratories, and recovery of viruses has been good. As a result, it has been possible to recognize quickly the occurrence of influenza outbreaks and to let physicians and the public know about the timing and virus strains involved in the outbreaks. Studies are underway, sponsored by the European Scientific Working Group on Influenza, to better define the impact of influenza in the European region. Hanspeter Zimmerman reported on the Swiss system of sentinel physician surveillance, which was developed so that attack rates could be generated for various regions of the country.

Other parts of the world are less well covered by laboratories, and in some extensive regions, especially in Africa, laboratories with the capability of identifying viruses simply do not exist. Contacts have been made to help develop laboratories in these regions so that if a pandemic strain arises in these vast areas, it may be detected. Various models may be adopted for this purpose; one that has proven successful would be to create ''twinning'' or sister laboratories. The developed country laboratory would adopt the facility in the less-developed country and provide advice for and assistance in improving capabilities. These efforts are not without costs in time, travel, and equipment.

The World Health Organization (WHO), through its collaborating centers in London, Atlanta, and now Melbourne, has taken the lead in working with a network of national laboratories. Alan Hampson described the history of WHO and the development of the concept of the networks of National Influenza Centres. However, at present, only ~60 countries have national centers, and these function at various levels of activity. While surveillance activity has increased in some countries, in particular China, it is important to realize that similar conditions for transmission exist in many areas of South and Southeast Asia and that it is impossible to obtain either specimens or data from these areas.

Another issue that needs to be considered in improving the collection of potential pandemic viruses is the substrate to be used. If eggs are not available, is there a cell line that can be used? Also, is that cell line going to be acceptable if the virus isolate turns out to be one that should be a candidate for the new vaccine and there is insufficient time available to isolate another representative virus in a suitable substrate? These issues need to be considered as laboratories with capabilities to collect and process specimens and to identify and characterize new isolates are recruited.

China remains a focus both in terms of dense population, which in the past had little sampling of influenza viruses, and the well-known likelihood that new pandemic strains arise from this region. Helen Regnery reviewed the existing virologic surveillance program in China, which has been organized and supported by the WHO collaborating center at the Centers for Disease Control and Prevention (CDC) in Atlanta since 1989. Currently, eight surveillance sites have been established in different geographic locations. Each site collects specimens from persons with acute respiratory disease and performs the initial isolation. After isolation, influenza viruses are transported to the Institute of Virology in Beijing, where samples are lyophilized and forwarded to the CDC for further characterization. Information provided with submitted specimens includes collection date, the patient's age and geographic location, and the extent of influenza activity in the area at the time of specimen collection.

Use of Surveillance Data to Control Pandemics

Other studies sponsored by various agencies have examined the occurrence of influenza viruses in domestic and other ani-

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Chair: Claude Hannoun; rapporteur: Nancy H. Arden; participants: Lars Haaheim, Alan W. Hampson, Arnold S. Monto, Kuniaki Nerome, Helen Regnery, Frederick L. Ruben, Kennedy F. Shortridge, and Hanspeter Zimmerman.

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mals in contact with human populations, particularly pigs and ducks. Kennedy F. Shortridge, of the University of Hong Kong, systematically reviewed the status of theory and fact surrounding the observation that influenza pandemics originate in China. This observation is based on the theory that pandemic influenza strains may arise through genetic reassortment when human and avian influenza type A strains infect a common host. Because the domestic pig is susceptible to infection with both human and avian strains, it is a likely host for such an event. Living conditions in South China, with animals and humans in close association, facilitate this possibility. With this background, it is important to design an ''early-warning system'' for the emergence of a novel virus, involving surveillance of animals as the likely source of pandemic virus and surveillance of human populations as recipients.

Dr. Shortridge reviewed the rationale for these recommended surveillance programs. Poultry, especially ducks, do not experience illness with infection but are documented to have an abundance of viruses of diverse hemagglutinin subtypes. Especially in view of the large numbers of poultry (>7000 million in 1993), a general surveillance program would not be likely to result in development of any useful information about transmittal of viruses to human populations. Data suggest that the presence of avian influenza viruses in pigs in southern China, while well-documented, is uncommon. The large size of the pig population, like that of poultry, presents a significant difficulty in any attempt to identify a prepandemic strain. An exception would be special studies of selected farming communities. In contrast, outbreaks of equine influenza occurring in China should be monitored. In this way, existing anecdotal information from Mongolia on transmission of influenza from horses to nomadic children could be confirmed or refuted.

Efforts to Improve Virologic and Disease Surveillance

As a result of these observations, Dr. Shortridge recommended concentration of efforts in China on human surveillance, with creation of an international pandemic influenza task force to be sited in China but administered though the WHO. For this effort to have full Chinese participation, a change in the way influenza is viewed in China will be required. Influenza is generally considered a relatively low priority cause of disease in humans. Until this changes, especially in the North, where seasonal influenza outbreaks are recognized, it will be difficult to mount the targeted surveillance of human infections necessary for early detection of potential pandemic viruses. It should also be remembered that China has changed enormously since the last pandemic, and any new pandemic virus will certainly move differently and probably more rapidly than in the past. In terms of the situation in Asia, Kuniaki Nerome described Japanese surveillance activities and proposed the development of special kits that include avian hemagglutinin reagents for identification of new pandemic strains.

Surveillance has been accomplished using different methods in areas of the industrialized world. Lars Haaheim reported on studies in Bergen, Norway, in which serologic methods were used before and after outbreaks of infection over a period of two decades. The purpose was an attempt to predict susceptibility to new strains and then to evaluate the impact of those strains on the population. The method has been valuable for the latter outcome but not for the former. That limitation should be kept in mind when planning surveillance activities.

Nancy Arden and Arnold Monto discussed surveillance activities in the United States. That surveillance has been based on virologic data from specimens received from health departments and clinical and research laboratories, morbidity data from sentinel practice sites, outbreak reports from schools and nursing homes, and mortality data characterized by pneumonia- and influenza-related deaths. It was emphasized that efforts are needed to enhance systematic surveillance of influenza-related morbidity in terms of attack rates in defined population groups, clinical characteristics of the illnesses, and frequency of complications, including outpatient visits and hospitalization. One mechanism for achieving this goal would be to take advantage of information collected by managed care organizations, which could also provide the opportunity for regular follow-up data. Collection of pneumonia- and influenza-related mortality data from death certificates has proven to be a satisfactory mechanism for studying influenza. Recent studies suggest that a greater effort should be made to examine total respiratory and ''all cause'' mortality as well. In addition, a more systematic approach should be developed to assess the impact of changes in the distribution and uses of vaccines and antivirals. Antivirals play a special role in control of pandemics; however, more information is needed on the effectiveness of and adverse reactions caused by antivirals and on the occurrence of resistant strains.

Charles Hoke discussed the role of the US military in influenza surveillance. The Air Force participates in global influenza surveillance by enlisting US and overseas bases that routinely collect and test throat-swab specimens from active-duty personnel and their dependents with acute respiratory illnesses; other military bases submit specimens when they detect an increase in respiratory illness. This system can augment the WHO international virologic surveillance by providing additional sites, especially in geographic areas where there is no WHO laboratory. Because a large proportion of military personnel receive influenza vaccine every year, rates of influenza infection are low when there is a good antigenic match between the vaccine and circulating strains. This provides an opportunity to quickly recognize antigenic changes in circulating strains, since outbreaks of influenza can be detected and investigated quickly.

Several participants talked about the need for better communications, and this area was summarized by Fred Ruben. The key here is a quick turn-around and the ability to inform and to reassure the public that appropriate measures are being taken. In addition, in the interpandemic period, it is vital to educate the public as to the importance of the threat of influenza so

that all education does not have to be undertaken when the pandemic is imminent.

Recommendations

On the basis of this discussion, the panel made the following recommendations for consideration by the National Institute of Allergy and Infectious Diseases, National Institutes of Health:

- *The number of sites conducting human surveillance should be increased, and the capacity of current sites conducting animal and human surveillance in East Asia, particularly in China and possibly in Russia, should be improved.*
- *Since large gaps in global surveillance of influenza exist, efforts should be made to strengthen both virologic and disease surveillance, possibly through the development of ''sister'' laboratories. This would include a more detailed system reporting such items as attack rates, clinical characteristics of illness, nature and severity of complications, and hospitalizations.*
- *The system of coordination with the US military surveillance system should be improved.*
- *Existing collaborations among agencies and international organizations, as well as local and country resources, need to be strengthened, especially to prepare for epidemiologic investigations of influenza outbreaks.*