Surveillance for Pandemic Influenza

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Concerns that a new influenza strain may arise that would exhibit similar properties to the 1918–1919 pandemic virus prompted the decision in 1947 to establish a World Health Organization global program for influenza surveillance. This program has contributed greatly to understanding of the epidemiology of influenza and provides the basis for the timely updating of influenza vaccine formulations during interpandemic periods. The spread of pandemic influenza, however, is extremely rapid and, in 1957 and 1968, occurred before sufficient supplies of vaccine could be prepared and administered. Recent evidence regarding the origin of new influenza strains provides some opportunities for improving surveillance for pandemic influenza, but there is a danger that the benefits may be offset by even more rapid spread of a future pandemic due to changes in worldwide transportation and commerce.

While national surveillance programs have an important role in monitoring the progress of both epidemic and pandemic influenza, it is the World Health Organization (WHO) global influenza surveillance program that will determine the timeliness of our response to a future pandemic. I propose, therefore, to review this global program in the context of lessons already learned and our current understanding of the particular issues that influence the needs of a pandemic surveillance program and its likely effectiveness.

Establishment of the WHO Surveillance Program

In 1947, only 12 years after the first successful cultivation of human influenza virus, a major antigenic change in the circulating influenza A strains was observed together with associated vaccine failures. While we now know that the virus is capable of more radical changes than that seen in 1947, the observation kindled concerns that the world might once again experience a devastating pandemic, such as occurred in 1918. As a consequence, a group of virologists met during the 4th International Congress for Microbiology held in Copenhagen in 1947 and forwarded a recommendation to the Interim Commission of WHO that an international program be initiated for influenza surveillance.

This recommendation was accepted at the fourth session of the WHO Interim Commission in September 1947, and the World Influenza Centre (WIC) was established at the National Institute for Medical Research (London), which was to work initially in close cooperation with a number of regional laboratories [1]. It was proposed that all countries might eventually have their own national influenza centers. The objectives of the WHO program were 2-fold: to gain an understanding of the epidemiology of influenza and to promptly isolate influenza viruses from new outbreaks and distribute them for vaccine production.

The functions of WIC were essentially the same as the terms of reference of the three current WHO Collaborating Centres for Influenza Reference and Research (London, Atlanta, Melbourne; hereafter called the collaborating centers) [2]: (1) collecting and distributing information about the types of influenza virus prevailing in various countries; (2) advising on the strains to be included in influenza vaccines; (3) collecting, preserving, and studying strains from various outbreaks and distributing them to interested laboratories; and (4) educating small numbers of visiting workers in techniques.

The surveillance program has now grown to include 110 designated National Influenza Centres (hereafter called national centers) in 80 countries and the 3 collaborating centers. National centers submit regular epidemiologic reports to WHO (Geneva) and, in many cases, forward virus isolates for antigenic analysis to 1 of the 3 collaborating centers. The collaborating centers carry out antigenic analysis of the strains received and do other studies that assist in the selection of vaccine strains, including sequence analysis of the viral antigens and determination of immunity to current isolates in the population at large and in vaccinated persons.

Since the initiation of the program, (1) it has been demonstrated that there are several distinct subtypes of influenza A, (2) we have witnessed two pandemics plus the disappearance and return of the H1N1 subtype, (3) nonhuman sources of influenza virus have been implicated in the origin of pandemic influenza, (4) there have been some significant changes in the way we carry out laboratory-based surveillance for influenza, and (5) there have been significant changes in world transportation and trade that may influence the spread of the disease.

Over the last few decades, operation of the WHO influenza network has become progressively focussed on the annual consultation on influenza vaccine formulation, which is held in
February each year—what we might refer to as epidemic surveillance. The program has demonstrated a high degree of success in matching vaccine strains to the circulating epidemic viruses. However, it is important to consider how well the network might cope if a new pandemic virus arose today, because there are important differences between pandemic and epidemic situations. I propose to concentrate particularly on what we now know about the geographic and biologic origins of pandemic viruses, the implications for pandemic surveillance, and the potential opportunities to improve on the existing global surveillance program. Finally, I will comment regarding the methods currently used in laboratory surveillance for influenza.

**Geographic Origins of Pandemic Influenza**

Through the activities of the WHO laboratory network, there is good information regarding the spread of the Asian (H2N2) and Hong Kong (H3N2) pandemic viruses in 1957 and 1969, respectively, and regarding the reemergent H1N1 virus in 1977, together with approximate locations of their origins. However, because influenza produces such a characteristic disease, we can also trace the putative origins and spread of many earlier episodes, some of which were clearly pandemics, although opinions vary as to which of the earlier outbreaks qualify as pandemics.

Historical accounts serve to illustrate some of the important features of pandemic influenza. Summaries of pandemics since the 18th century and their probable geographic origins published by Patterson [3] and Beveridge [4] suggest that the majority of these arose in China, although central (Asian) Russia may have been the source of some earlier episodes (table 1). However, there are also suggestions that those may also have originated in China—the major pandemic in 1781–1782, for example, was referred to by the Russians as Chinese catarrh. This 1781–1782 outbreak followed the characteristic progression of these early pandemics from central Russia westward through Europe along the major trade routes of the day. The pandemic spread throughout western Europe during the summer of 1782, demonstrating that pandemic influenza can occur at any time of year and is not restricted to the autumn and winter months, when interpandemic outbreaks are normally experienced in temperate regions.

The great pandemic of 1918 is probably unique among the influenza pandemics of the last 200 years, as its origin remains obscure. This particular pandemic is also unique for a number of other reasons—the extremely high death rate, the age distribution of its victims, and the fact that it occurred in three clearly defined waves in most parts of the world. The transport of large numbers of troops and laborers between the United States and Europe and other parts of the world during World War I was instrumental in the spread of this pandemic and may well have masked its true origin. There is a suggestion that an early epidemic occurred in Chunking, China, during July 1918, and this, together with the movement of large numbers of Chinese laborers into Europe, may account for a Chinese origin for this pandemic; however, this is a tenuous association [5]. The fact that the pandemic appeared in three successive waves of quite different mortality is interesting in view of the molecular evidence, referred to below regarding the origins of the virus; it appears that the virus appeared first in a relatively mild form, acquired its increased lethality on passage in humans, and then settled down to a less lethal form.

Despite the wealth of historical information on influenza pandemics, our most detailed data come from the two pandemics that have occurred in the era of laboratory diagnosis. The 1957 (Asian) pandemic virus was first detected in Hong Kong in April and was quickly recognized as a new influenza A subtype. During May, the virus had already reached Japan and Southeast Asia, and by June, it was found on the West Coast of the United States. In Japan, there were two epidemics: the first in May through July and the second in September through December. While the virus spread into the North Temperate Zone during spring and summer, in many cases the major outbreaks did not occur until autumn. A number of countries, including the United States, reported two waves in this pandemic [6]. Retrospectively, the first detection of the new virus was in southwestern China, where the disease was seen in February [7]. Apparently, the virus reached the outside world by two routes: along the Trans-Siberian Railway into the (then) USSR and by sea from Hong Kong to Singapore and Japan.

The first indication of the 1968 (Hong Kong) pandemic virus was a report in mid-July of an outbreak in southeastern China; this was followed a short time later by a sudden increase of influenza-like disease in Hong Kong. The spread of the 1968 virus was initially very similar to that of the 1957 virus, with epidemics in Singapore and other Southeast Asian countries in August. In Japan, the virus was introduced in September but failed to produce an epidemic until January [8]. The impact of the Hong Kong virus varied quite widely, with relatively little impact in much of Europe and Canada during 1968–1969. In

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**Table 1. Influenza pandemics recorded since 1700.**

<table>
<thead>
<tr>
<th>Year(s)</th>
<th>Origin</th>
<th>Virus type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1729–1730</td>
<td>Russia</td>
<td></td>
</tr>
<tr>
<td>1732–1733</td>
<td>Russia</td>
<td></td>
</tr>
<tr>
<td>1781–1782</td>
<td>Russia/China?</td>
<td></td>
</tr>
<tr>
<td>1830–1831</td>
<td>Russia/China</td>
<td></td>
</tr>
<tr>
<td>1833</td>
<td>Russia</td>
<td></td>
</tr>
<tr>
<td>1889–1890</td>
<td>Russia (Asia)</td>
<td>H2</td>
</tr>
<tr>
<td>1899–1900</td>
<td>?</td>
<td>H3*</td>
</tr>
<tr>
<td>1918–1919</td>
<td>USA/France?</td>
<td>H1N1</td>
</tr>
<tr>
<td>1957</td>
<td>China</td>
<td>H2N2</td>
</tr>
<tr>
<td>1968</td>
<td>China</td>
<td>H3N2</td>
</tr>
<tr>
<td>1977</td>
<td>China</td>
<td>H1N1</td>
</tr>
</tbody>
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* Listed by Patterson but not by Beveridge.

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NOTE. After Patterson [3] and Beveridge [4].
the United States, however, the virus spread from an initial outbreak in California in October from west to east across the country, with a peak around Christmas and a high mortality rate. Most Southern Hemisphere countries did not suffer major outbreaks until May and June 1969. In 1968, the Hong Kong virus was isolated, characterized, and made available through the WHO program to vaccine producers by mid-August.

Although not classified as a true pandemic, the reemergence of the H1 subtype of influenza A (which was called Russian influenza) in 1977 is worth mentioning. The first reports were of outbreaks occurring in schools in Russia during November 1977; by December, it had reached most of the large cities in Siberia and the European part of the (then) USSR [9]. The virus spread a little more slowly than the Asian and Hong Kong strains and affected mainly younger members of the population. Retrospective reports indicated that the first outbreaks occurred in Tientsin, China, in May 1977 [10].

From these observations, it has been concluded that there may be what has been referred to as an “influenza epicenter” in China [11]. It is also clear that the virus spreads very rapidly and tends to be less constrained by season than the usual epidemic viruses; however, there may still be some seasonal influence, and this may be the reason that two waves of infection are often experienced. Unfortunately, we still have no good information about the time course of spread of the virus from its initial source until it is first seen as epidemic outbreaks.

Biologic Origins of Pandemic Influenza

The second important factor for pandemic surveillance is the biologic origin of pandemic strains of influenza A. It has become progressively accepted over the last 2 decades that influenza viruses from animals and birds are involved in this process, and I shall give a brief overview of our current understanding of these events. The major surface antigen of influenza A, hemagglutinin, has been shown to exist in 15 distinct forms or subtypes, and the minor antigen, neuraminidase, in 9 forms [12]. It would now appear that aquatic birds, particularly ducks, are the primary host of influenza A viruses, and all of the hemagglutinin and neuraminidase subtypes are found in them. A small number of subtypes have become established in mammalian species, and from time to time there is evidence that an avian virus has crossed into a mammalian species [13].

We know that humans have been host to 3 influenza A hemagglutinin types during the last century, and each of these has occurred on two separate occasions. Genetic analysis shows that the 1957 and 1969 viruses arose by genetic reassortment between the previously circulating human influenza strains and an avian virus, such that the reassortant virus in both cases received the hemagglutinin and one nonstructural gene of the avian virus and, in the case of the 1957 virus, the neuraminidase also. The fact that the Hong Kong virus had a common neuraminidase with the preceding subtype may account for the slightly lesser impact of this virus in some countries.

While recent surveillance and some past experience indicate that avian viruses can cross the species barrier into horses, pigs, and sea mammals, sometimes with dramatic results, there is little direct evidence of avian viruses productively infecting humans. In fact, there is laboratory evidence that the nucleoprotein of influenza viruses may dictate the species specificity of human and avian influenza, although viruses with either form of the nucleoprotein are known to replicate in pigs [14]. It is widely accepted that the pig could act as a genetic “mixing vessel” for the formation of new pandemic strains by genetic reassortment between human and avian viruses; however, to date, only the H1 and H3 subtypes have been found in pigs.

On the other hand, genetic study or genetic archeology on the H1N1 descendants of the 1918 virus isolated during the 1930s suggests that this virus was not formed by reassortment but rather by adaption of an avian virus to humans. It has been suggested that this may have occurred following adaption in the pig as an intermediary [13]; this may be consistent with the apparently different geographic origins of the 1918 virus. There is no doubt that influenza viruses from pigs can infect humans and cause disease. This was demonstrated at Fort Dix in the United States in 1976 with the outbreak of A/New Jersey/76 virus, which was clearly derived from swine influenza virus [15], and again recently in Europe, where there are two examples of transmission of human avian reassortant viruses from pigs to humans [16]. Because of the evidence of animal and avian involvement, WHO developed an informal program to coordinate studies on the relevance of animal and avian influenza to human disease and in 1983 designated R. G. Webster’s laboratory as a WHO Collaborating Centre for Studies on the Ecology of Influenza in Animals [17].

One of the main questions that arises from our experience to date is whether the hemagglutinin of influenza virus may also contribute in some manner to host range restriction for humans. Is it possible that only the H1, H2, and H3 subtypes will ever be found in humans? Shortridge’s work [18] may tempt us to believe not, as studies conducted on sera from various regions in China do show considerable evidence of antibody responses to a range of subtypes of influenza. The presence of an antibody response implies some replication of the virus in humans, even though this may be limited and inadequate for further transmission. As most of these subtypes have yet to be detected in the pig, it seems probable that humans have been infected directly from birds, implying that there would be an opportunity for reassortment to occur directly in humans with existing human strains.

Requirements for Pandemic Surveillance

With respect to pandemic surveillance, the two primary goals of the WHO global program are to gain an understanding of the epidemiology of influenza and to promptly isolate influenza viruses from new outbreaks and distribute them for vaccine production.
These goals are as relevant today as they were in 1947; however, our success in dealing with a pandemic situation will depend on the time frame in which we can accomplish the second goal. As noted earlier, our current surveillance is very much tailored to the epidemic situation; comparing the spread of a recent epidemic strain (A/Beijing/32/92) with the Hong Kong pandemic virus and the reemergent H1N1 strains emphasizes the markedly different time frames in which we must work (figure 1). It is worth remembering, however, that in both 1957 and 1969, the new strains were isolated and available to vaccine manufacturers within 6 weeks of the first outbreaks outside of China, and vaccine manufacture proceeded quickly. In the United States in 1957, almost 50 million doses of vaccine had been released by the time the epidemic peaked late in the year [19].

If the rate of spread of the last two pandemics is alarming, it seems certain that the next will spread even faster. If we consider China to be a likely source of the next pandemic, the relaxation of trade and tourism restrictions in that country will surely spread the virus to other countries even more quickly than in the past. There is a particular risk of the next pandemic virus emerging through Southeast Asia, where our current surveillance is particularly poor. In addition, the vastly increased air passenger services between countries must mean that the virus will spread around the globe more quickly than before. In 1986, Longini et al. [20] reported applying, to the 1968–1969 pandemic, a predictive model for spread of influenza virus that had been developed in the (then) USSR some years earlier. The model showed a high level of predictive accuracy for the epidemic period in a number of major cities. The authors suggested that global modeling should be carried out in an international context, perhaps within existing surveillance programs of WHO. Modeling the spread of an influenza pandemic today using current passenger data might provide an interesting insight into the extent of the problem we will face.

What can we do to maximize the time available and the speed of our pandemic response? First, we should fill in some of the gaps in the surveillance network, particularly in what we might term high-risk countries, where conditions may favor animal-to-human transmission. Currently only ~75% of the 110 listed WHO national centers are active, and these represent only 60 countries with active surveillance programs. On the other hand, recent surveillance in China has been significantly improved by the availability of virus isolates for analysis from eight regional laboratories. These represent northern, central, and southern regions of the country but tend to be concentrated toward the east. How can surveillance of human influenza outbreaks be further improved in China? Would it be more effective to recruit additional contributing laboratories or to improve outside of China, and vaccine manufacture proceeded quickly. In the United States in 1957, almost 50 million doses of vaccine had been released by the time the epidemic peaked late in the year [19].

On the other hand, we should not become preoccupied with China as a possible influenza epicenter. The dubious origin of the 1918 virus, the Fort Dix episode, and the recent demonstration of transmission from pig to human in the Netherlands highlights the possibility that a new pandemic virus could arise virtually anywhere humans have close contact with birds or mammals that carry the virus. A number of areas where this could occur have little or no active surveillance.

For example, in November 1993, the collaborating center in Australia received reports of an outbreak of influenza-like illness in a remote region of Papua New Guinea. Some 3000–4000 cases had occurred over a 3-month period, with >200 deaths among the very young and very old. Despite our best efforts, we were unable to obtain any material for study (clinical specimens or postinfection sera), although an epidemiologist did travel to the area and reported that the outbreak was consistent with influenza. The outbreak failed to spread beyond the New Guinea highlands; however, the domestic pig plays an
important role in village agriculture in Papua New Guinea, and it is not unthinkable that transmission of influenza viruses between human and pig occurs there and in many other developing countries where there is little or no surveillance.

There are many impediments to improving the surveillance network, including lack of finance, trained scientists, and the necessary infrastructure in the countries concerned. In addition, influenza is a relatively low priority in many developing countries where there are more pressing and visible health concerns.

It is hard to imagine that, under today’s conditions, the next pandemic virus will not be quickly transmitted beyond its source. The fact that the earliest apparent outbreaks of the 1957 Asian virus in China were only 2–3 months ahead of those in Japan and Singapore suggests that increased surveillance of human influenza outbreaks in high-risk regions can have only a marginal effect on the overall time frame.

Are there other ways in which surveillance might provide a longer time frame for our response? Is there a period when a new pandemic strain passes slowly through the population, becoming progressively adapted to the human host, or does it arise with full disease potential and transmissibility at the outset? The second, more severe outbreak in some pandemics suggests that the virus may progressively adapt to humans. If this is the case, is there any value in extending our surveillance to other indicators of human infection with new subtypes, such as the antibody studies reported by Shortridge [18]?

If, as it seems, the domestic pig does indeed play an important role in the origin of human pandemic viruses, then surveillance for evidence of new hemagglutinin types in pigs and, in particular, of human-avian reassortant viruses might allow us to anticipate the emergence of a new strain. If we were to assume that any of the avian hemagglutinin subtypes could yield the next pandemic virus, could we not use surveillance of the avian strains to provide us with potential vaccine strains? In the case of H2 and H3 viruses, the putative avian progenitor hemagglutinins were extremely closely related antigenically to the emerging viruses [21, 22]. There is the potential to save several weeks in a vaccine production program by preparing validated high-growth strains and the reagents for vaccine standardization. Finally, a key element in ensuring a timely response within our global program must be to have a defined mechanism and criteria for declaring a pandemic situation.

**Laboratory Methods of Surveillance**

Some comments on laboratory methods of surveillance are also justified, as these may also be important in the context of our pandemic response. In the collaborating centers, many of our “bread and butter” methods for analysis of influenza virus isolates are little changed from those in use at the time the WHO global program was initiated. We use the hemagglutination-inhibition test for antigenic analysis of isolates, embryo-nated eggs to grow our reference antigens, and infection of ferrets to raise our polyclonal reference sera. However, in many of the laboratories dealing with clinical specimens, there have been quite significant changes. For example, monkey kidney culture progressively replaced embryo-nated eggs as the preferred culture system for isolating influenza viruses, and then for practical and ethical reasons, the MDCK cell line replaced monkey kidney cells [23].

The great majority of virus isolates available for analysis are now cell culture isolates, and these have yet to gain regulatory acceptance for use as a vaccine. This carries the risk of an additional delay between recognition of a new pandemic strain and its availability in a form acceptable for vaccine use. This delay, together with the demonstrated host-adaptive change that accompanies direct egg-isolation of influenza viruses, suggests that we should take steps to validate the standard laboratory culture system for influenza virus as a source of vaccine strains. It may be fortunate that, for the moment, a few laboratories, including those in China, continue to use the embryo-nated egg for the isolation of influenza viruses.

In addition, for some time it has been possible to make a definitive laboratory diagnosis of influenza by direct antigen detection methods, IFA, and EIA, and these are sufficient for the majority of clinical diagnostic laboratories. As a result, many influenza A infections are not subtyped, and a new subtype may initially go undetected. A sensitive, rapid, and inexpensive direct antigen detection method that could identify an influenza A virus and differentiate H1, H3, and non–H1–H3 subtypes, similar to the rapid culture assay described recently [24], would be invaluable for pandemic surveillance.

Finally, it seems appropriate to conclude with the words of Justin M. Andrews, Director, National Institute of Allergy and Infectious Diseases, in his foreword to the report of an international conference on Asian influenza held in 1960 [25].

Through the years, man’s life has been dramatically influenced by the sudden appearance of influenza in epidemic and pandemic forms. On each such occasion medical science has bestirred itself to study the disease intensively. Traditionally, however, within a short span of time thereafter the upsurge of interest in influenza research has begun to wane, leaving only a few scientists with special research interests to continue the elucidation of this particular disease. In spite of this feast-or-famine approach, much has been learned and large strides have been taken toward a more complete understanding of the disease process.

I hope the current meeting will encourage us to bestir ourselves ahead of rather than after the next pandemic.

**References**