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Influenza: Global surveillance for epidemic and pandemic variants

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Abstract. Influenza viruses, unlike other viruses for which vaccines have been developed, undergo rapid and unpredictable antigenic variation in the hemagglutinin (HA), the surface glycoprotein primarily responsible for eliciting neutralizing antibodies during infection. Because of this antigenic variability and its consequences, the World Health Organization (WHO) in 1947 established an international network of collaborating laboratories to monitor the emergence and spread of new epidemic and pandemic strains of influenza. This network now includes three international WHO collaborating centers and over 100 WHO national collaborating laboratories. The primary purpose of this network is to detect, through laboratory surveillance, the emergence and spread of antigenic variants of influenza that may signal a need to update the formulation of the influenza vaccine. This laboratory surveillance network has provided the strains needed to update the vaccine as well as a repository of influenza viruses useful for studying the antigenic and genetic evolution of this virus. Knowledge gained from molecular studies on the evolution of drift variants and on the emergence of pandemic strains has made influenza a useful model for understanding the potential threat of other emerging or reemerging microbial diseases.

Key words: Influenza surveillance, Influenza variants, Influenza vaccine

In the United States, global surveillance activities are coordinated by the WHO Collaborating Center for Surveillance, Epidemiology, and Control of Influenza, located at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. Epidemiologic information and influenza isolates are received at the CDC from a variety of domestic and international sources. This information and laboratory data are analyzed and then disseminated through national and international networks. Here we will describe the US domestic surveillance network. In addition, we will describe a relatively new influenza surveillance program in China and the detection by the global surveillance network of an influenza variant (A/Beijing/353/89) that was included in the vaccine before it caused widespread epidemic activity in Europe and North America. We will also describe how molecular evolution studies have improved our ability to select the most relevant strains for inclusion in the vaccine.

Domestic influenza surveillance is important because it provides the most complete information available to us concerning the extent and severity of influenza activity, the characteristics of the circulating strains, and the clinical effectiveness of the vaccine. The components of the US influenza surveillance system include: (1) approximately 68 US WHO collaborating laboratories that report weekly the number and type of influenza viruses isolated and send representative viruses for characterization, (2) state and territorial health departments that report the level of influenza activity occurring each week, (3) a network of sentinel family physicians that report the proportion of patients seen for influenza-like illness each week, (4) vital statistics offices of 121 US cities that report weekly the percentage of total deaths caused by influenza and pneumonia, and (5) a variety of other sources that report influenza outbreaks or other influenza associated problems. This surveillance has shown that influenza epidemics with associated excess mortality have occurred in the USA in at least seven of the last ten influenza seasons and that the most severe epidemics have often occurred when the majority of the viruses circulating were of the influenza A (H3N2) subtype. It has been estimated that as many as 40,000 total excess deaths and 200,000 excess hospitalizations may have occurred in the USA during such epidemics [1]. Epidemics like these caused by drift variants of influenza are costly because they occur frequently. The social and economic impact of the emergence of a new pandemic strain, however, is potentially much larger.

Historical accounts of influenza pandemic and epidemic activity indicate that variant viruses have often emerged in China. It has been well documented that the each of the last three pandemic strains of influenza originated there (reviewed in [2]). In addition, there has been growing circumstantial evidence that drift variants of influenza might also

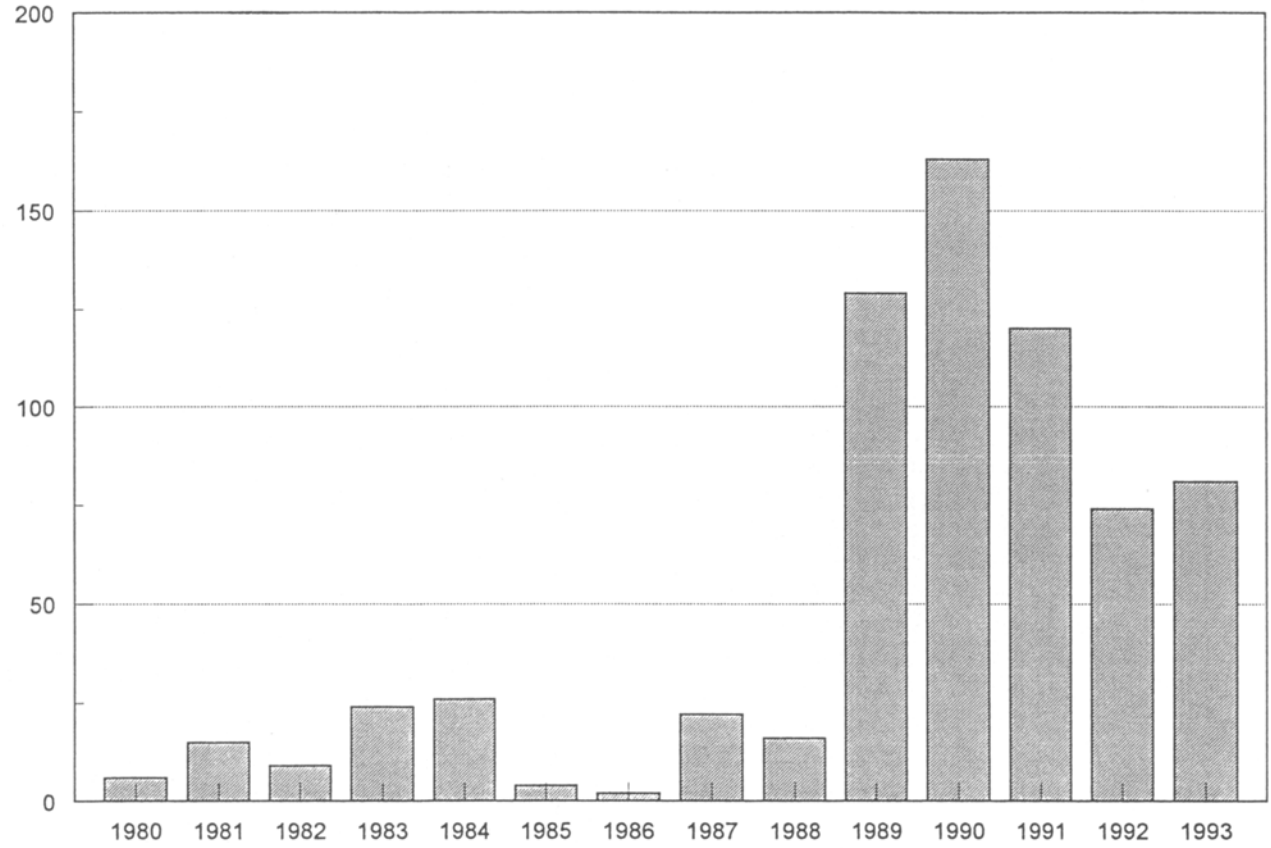
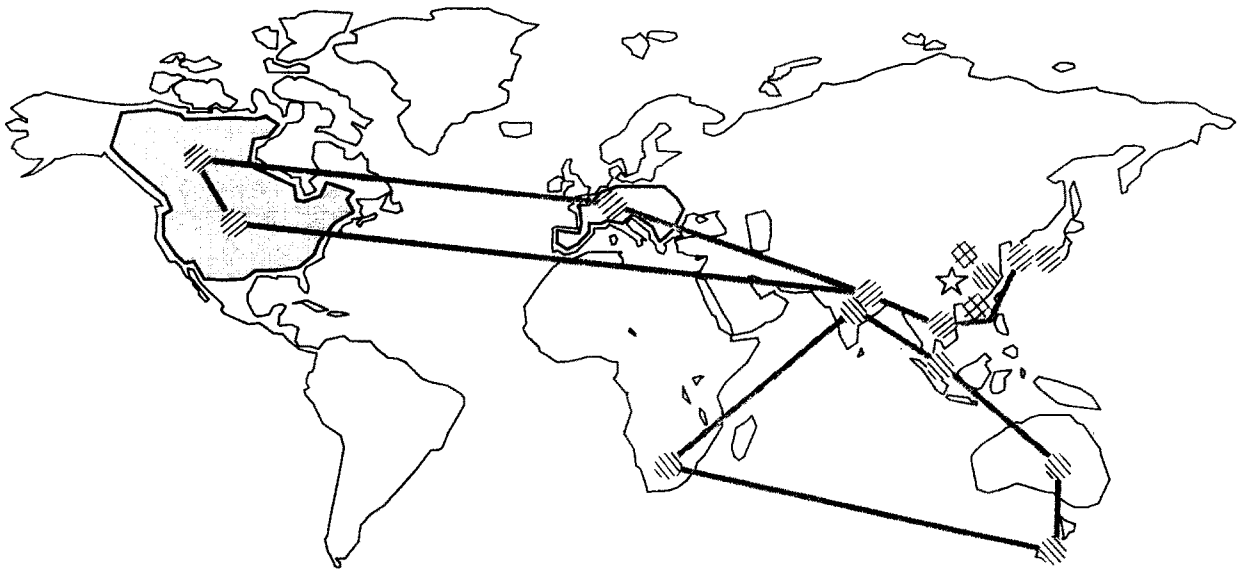


Figure 1. Number of influenza isolates from China, received during the calender years 1980–1993.



☆ - Isolation of A/Beijing/353/89-like virus, Nov. 1989
Nov. 89 - Mar. 90 ⊠ - China, Hong Kong
Apr. 90 - Sep. 90 ▨ - China, Singapore, India, South Africa, Australia, New Zealand
Oct. 90 - Mar. 91 ▨ - Japan, Korea, Thailand, India, USA, Canada, Europe
Apr. 91 - Mar. 92 □ - Epidemic Level Activity USA, Canada, Europe; Sporadic Isolates Worldwide

Figure 2. Spread of A/Beijing/353/89-like (H3N2) viruses 1989–1991. Source: CDC.

emerge first in China or neighboring countries. These observations prompted CDC to provide resources for a national influenza surveillance system in China and thus increase the number of influenza viruses from China available for analysis by the WHO network. The success of this program can be demonstrated by the increase in the number of influenza viruses sent from China for analysis since 1988–89 when the program began (Figure 1). The importance of this program is underscored by the fact that the three most recent influenza A(H3N2) variants (A/Shanghai/11/87-like, A/Beijing/353/89-like, and A/Beijing/32/92-like strains) that caused epidemics in Europe and North America were detected first in China through this program and were recommended by WHO for inclusion in the trivalent influenza vaccine [3, 4, 6].

Following is an account of the emergence and apparent spread of the A/Beijing/353/89 variant. During the 1989/90 influenza season when A/Shanghai/11/87-like influenza A (H3N2) viruses caused severe epidemics in Europe and in the USA, several distinct variants of influenza A(H3N2) viruses emerged [4]. One of these, the A/Beijing/353/98 variant was detected first in central China in November of 1989. This variant was subsequently detected in northern China during December and January and in southern China during March, April, and May of 1990. From April to September of 1990, this variant was detected outside of China in India, South Africa, Australia, and New Zealand. Between October 1990 and March 1991, A/Beijing/353/89-like viruses were detected at low levels in Japan, Korea, Thailand, the United States, the Netherlands, Switzerland, and Canada (Figure 2), during a year when influenza B viruses predominated worldwide. Because A/Beijing/353/89-like viruses had caused outbreaks or sporadic cases with a widespread geographic distribution, this virus was chosen for inclusion in the 1991/92 influenza vaccine. As evidence from worldwide surveillance had suggested, epidemics in Europe and North America were caused by A/Beijing/353/89-like viruses during the 1991/92 influenza season [5]. This illustrates how surveillance in China coupled with tracking variants through the WHO surveillance network can provide a good match between the circulating strain and the vaccine strain.

In addition to the reference antigenic analysis, molecular analysis is carried out on influenza viruses of interest. For the past 8 years, the hemagglutinin genes of potential vaccine candidate strains (and a variety of other strains) have been sequenced in order to determine their relationships to previous epidemic strains and to other potential vaccine candidates. Genes coding for other influenza virus proteins have also been sequenced for viruses of particular interest. These molecular studies have greatly enhanced our understanding of the evolution of influenza viruses and have provided data that are useful in the process of strain selection. They have also shown that reassortment between influenza A subtypes continues to play a role in the evolution of influenza viruses, that epidemic strains do not always evolve from previous epidemic strains, and that the overall rates of evolution for influenza A and B viruses are similar [7].

When the emergence and spread of a new antigenic variant of influenza are detected, a variety of organizations must work together in order to provide vaccines containing the new strain. These organizations include the WHO headquarters in Geneva, the three WHO international collaborating centers, the WHO national collaborating centers, the National Institute for Biological Standards and Control and other European national regulatory agencies, the Food and Drug Administration, the National Institutes of Health, academic researchers, and vaccine manufacturers. The interaction of individuals from these institutions occurs on a regular basis during the annual reformulation of influenza vaccines and also would be essential after the recognition of a newly emerging pandemic influenza virus. This regular interaction centered around selection of the most appropriate influenza strains for inclusion in the vaccine and the subsequent production of appropriate influenza vaccines each year has kept the WHO influenza network active for over 45 years. It must be kept in mind, however, that although the WHO influenza surveillance network has been quite successful and is often cited as a model for global surveillance, there is room for improving this network. For example, we must not miss opportunities to strengthen the infrastructure of this network, particularly in China and other countries in the Pacific Basin where new strains of influenza are most likely to be detected first.

Influenza viruses pose a constant threat to public health, whether in the form of antigenic drift variants or of totally new pandemic strains. Only through expanded global influenza surveillance can we hope to have an early warning system that will detect newly emerging viruses in time to prepare vaccines and other prevention strategies.

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