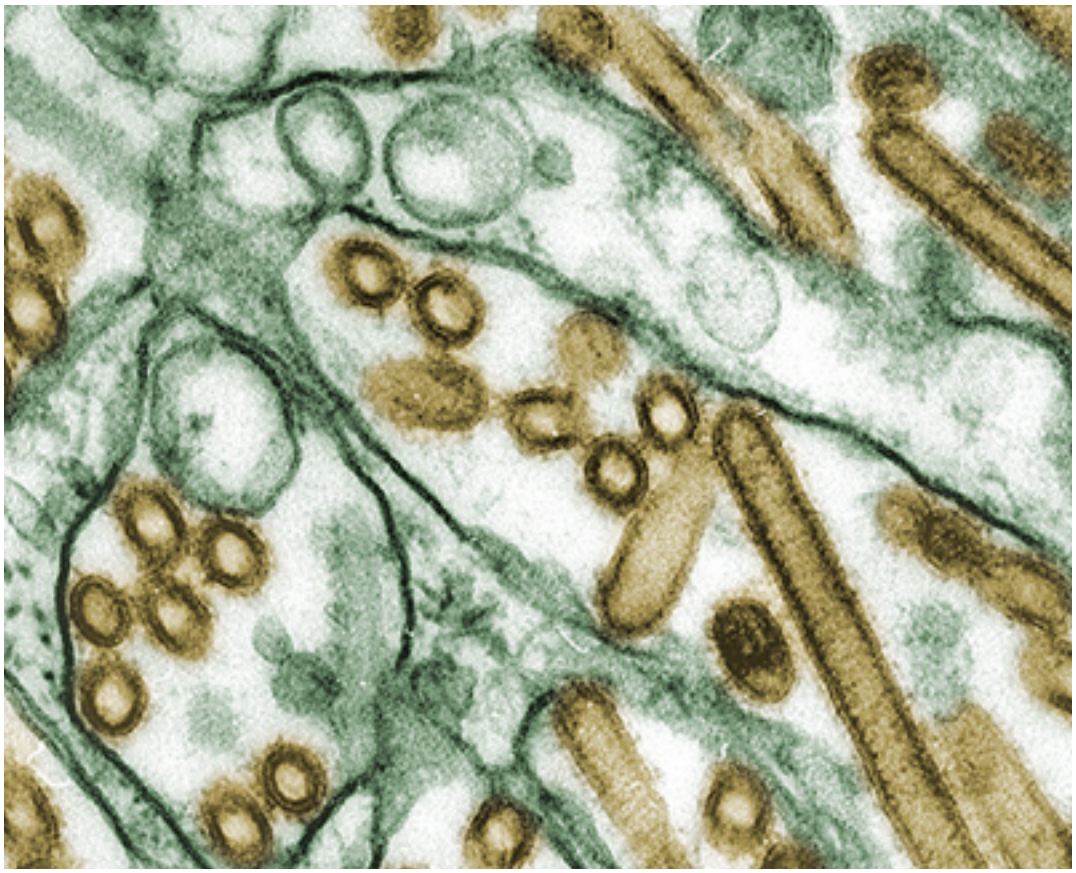
How the World Fights the Flu

Wenqing Zhang



CDC/Courtesy of Cynthia Goldsmith, Jacqueline Katz, and Sherif R. Zaki

This colorized, microscopic view depicts the avian influenza H5N1 virus in gold, grown in another cell medium shown in green. Increasing numbers of human infections from H5N1 occurring since 2004 caused health officials to become concerned that this virus, or one like it, has the potential to spark a global influenza pandemic with widespread human, social, and economic costs.

The World Health Organization coordinates a global effort to monitor seasonal and avian influenza emergencies for the production of vaccines that can help prevent and ease illness affecting hundreds of millions of people worldwide each year.

Wenqing Zhang, MD, is project leader for the Influenza Virological Surveillance and Vaccine Viruses of the Global Influenza Programme of the World Health Organization, based in Geneva, Switzerland.

Every year more than 250 million doses of influenza vaccine are produced that help to protect the world's population against influenza infections. For more than 50 years, the process by which an effective vaccine is developed and manufactured has relied on the international cooperation of a wide range of public health partners brought together under the coordination of the World Health Organization (WHO) in the Global Influenza Surveillance Network.

Influenza is caused by a virus that is passed easily from person to person, most often through droplets and aerosols created by people when they cough or sneeze. Usually the virus infects mainly the upper respiratory tract, the nose, throat, and bronchi, but in severe cases, the virus can spread to the lungs. Most people recover within one or two weeks without the need for medical treatment; however, for the very young, the elderly, and those suffering from

WHO Photo/Garrett Smythe

Virus samples are prepared at one of the National Influenza Centres participating in the global network of laboratories monitoring annual changes in influenza viruses.

certain medical conditions, influenza can pose a serious risk to health and can result in other complications such as pneumonia and even death.

Influenza causes outbreaks and infections throughout the world. In regular "seasonal" epidemics, up to 15 percent of the population can be affected, resulting in up to 500,000 deaths every year. In the tropics, influenza outbreaks occur year-round. The principal and most effective measure for preventing influenza is annual vaccination. Influenza vaccines have been in use for more than 60 years, and they have been proved safe and effective in preventing both mild and severe outcomes of influenza. Each year, it is thought, influenza vaccines can reduce the risk of serious illness or death in the elderly and reduce illness by up to 90 percent in healthy adults, resulting in substantial health and economic benefits.

The antigenic properties of a virus are the characteristics that will induce the response of the body's immune system to infection by the virus. By their very nature, influenza viruses are constantly undergoing antigenic changes. This means that the composition of influenza vaccines must be reviewed and adjusted each year to ensure that they match the antigenic properties of the viruses in circulation.

A Global Network

Worldwide monitoring of influenza viruses through surveillance is the mechanism by which the evolution of circulating viruses can be monitored. In 1952 a WHO expert committee recommended the establishment of an extensive international network of laboratories to conduct the necessary surveillance and provide WHO with the information it required to advise its member states on the most effective influenza control measures. The WHO Global Influenza Surveillance Network, or GISN, has been in operation ever since, functioning in all regions of the world under the coordination and administration of WHO headquarters.

GISN now includes more than 110 National Influenza Centres (NICs) located in 87 different countries and areas around the world, as well as four highly specialized WHO Collaborating Centres for Reference and Research on Influenza. These four Collaborating Centres are located in Atlanta, Georgia, United States; in London, United Kingdom; in Melbourne, Australia; and in Tokyo, Japan. Another Collaborating Centre in Memphis, Tennessee, United States, is focused primarily on studying the ecology of influenza in animals.

The NICs are the backbone of GISN. They are laboratories that have been designated by their country's top health officials as the national focal point for influenza surveillance with the necessary capacity and expertise to perform their role. An NIC is responsible for collecting or receiving specimens and viruses obtained from patients who are ill. Every year more than 175,000 clinical specimens are collected from patients worldwide. Some of these specimens yield viruses through a process known as viral isolation. The NIC undertakes a preliminary analysis and then forwards some virus isolates thought to be representative of viruses circulating in the population to one of the four specialized Collaborating Centres for further characterization.

An NIC is the key point of contact between WHO and a given country's health authorities on any matter regarding the surveillance of influenza. The NIC informs

WHO and other members of GISN about viruses in circulation, unusual viruses that may have been detected, and important or unusual outbreaks. It produces weekly reports on influenza activity in the country during the influenza season, which are published in the WHO *Weekly Epidemiological Record [www.who.int/wer]*, and provides information on the influenza epidemiological situation to FluNet *[www.who.int/flunet]*, a Web-based tool for the support and coordination of national and global influenza surveillance and reporting.

Many NICs also provide training and technical support to other network members in the region on the collection of specimens and the preliminary characterization of influenza viruses.

Ensuring Effective Vaccines

The four specialized WHO Collaborating Centres receive influenza virus isolates from NICs around the world and conduct advanced analysis of the antigenic and genetic profile of the viruses. This information helps to assess the significance of the antigenic changes among recent circulating viruses and determines whether current viruses differ substantially from existing vaccine viruses. The centres also help to monitor the evolution of the viruses and their ongoing susceptibility to influenza antiviral drugs. They also conduct serological studies in collaboration with other key national reference laboratories, such as the Center for Biologics and Evaluation and Research of the Food and Drug Administration in the United States, the National Institute for Biological Standards and Control in the United Kingdom, and the Therapeutic Goods Administration of Australia. In these serological studies, the antibodies that develop in response to current influenza vaccines are tested to ascertain whether viruses contained in the vaccines still match circulating viruses. That information is critical to knowing whether the existing composition will need to be updated in order to have an effective vaccine for the next season.

Twice a year, WHO convenes a consultation between the Collaborating Centres and the key reference laboratories involved in influenza vaccine selection and development to review the results of recent analysis. WHO is then able to recommend which influenza viruses should be used in the development of influenza vaccines

Vaccine Milestones: Smallpox Is Dead

U.S. National Archives Photos

This case of smallpox was "made mild" by a vaccination, according to the caption on this undated photo from the U.S. Army Medical Museum.

The most dramatic vaccine success story in the more than 200-year history of vaccines is the eradication of smallpox in 1980. Smallpox was targeted for eradication for several reasons: It was transmitted from human to human and had no animal reservoir; an effective heat-resistant freeze-dried vaccine existed that could protect in a single dose; and practical diagnostic tools were available for the ready identification of smallpox infection.

The World Health Organization adopted the goal of eradicating smallpox in 1959, but progress was fairly slow until the Intensified Global Eradication program was launched in 1967. The strategy was to launch mass vaccination campaigns in each country, ensure the potency and stability of the vaccine, and cover at least 80 percent of the population. Those campaigns were followed by rigorous disease surveillance to detect outbreaks and target them with focused containment measures. Whenever an "index" case of smallpox was reported, all close contacts of the index case were vaccinated, and then all close contacts of those people would also be vaccinated. This method effectively isolated the index case and broke the chain of transmission.

The last case of smallpox was identified in Somalia in 1977. The search for smallpox cases lasted for another two years, and in 1980, the World Health Organization declared that "smallpox is dead!" ■

Elizabeth Fee, Ph.D., National Institutes of Health

© AP Images

The U.S. health care sector goes to great lengths to encourage immunization against seasonal flu. Volunteers assisted the Oklahoma City-County Health Department in a mass flu immunization exercise as the 2006 flu season began. Cars lined up at an immunization drive-through, allowing the inoculation of more than 1,700 people in a few hours.

for the next season for each the northern and southern hemispheres.

The Collaborating Centres provide extensive training for laboratory staff from National Influenza Centres and other laboratories. Every year the centres update the standard antigens and sera used by the NICs in the network to diagnose seasonal influenza and provide advice as needed on the most appropriate and up-to-date laboratory methods for the diagnosis of influenza. The centres can provide assistance to countries on responding to an outbreak of influenza, particularly if it should have pandemic potential. They also provide WHO with recommendations and guidance on how to improve the global system of influenza surveillance.

A New Challenge

Recently the emergence of a new, highly pathogenic strain of the influenza virus, H5N1, has raised alarms that an influenza pandemic may be imminent, with the potential to cause high levels of illness and death and widespread social and economic disruption. This has presented the surveillance network with significant technical and operational challenges that fall beyond its established role in detecting and protecting against seasonal influenza.

H5N1 differs substantially from seasonal influenza viruses. It is a newly emerging animal virus that is highly pathogenic in poultry and has crossed the species barrier to infect humans. Handling the virus requires higher levels of laboratory containment, and few NICs have the necessary experience required to diagnose H5N1 infection or to respond to H5N1 outbreaks. As a result, much of the heavy workload of the NICs has been falling on the Collaborating Centres. In 2004 WHO established an ad hoc network, known as the WHO H5 Reference Laboratories, to help with diagnosing human H5N1 infections. This move will allow the Collaborating Centres to continue to conduct more advanced analysis of H5N1 viruses to assess the risk of pandemic and to develop the necessary diagnostic reagents (substances used to detect or measure H5N1), test protocols, and candidate H5N1 vaccine viruses.

In its more than 50-year history, the Global Influenza Surveillance Network has played a central role in global efforts to address influenza in all of its forms and has proven itself to be an exemplary model of international cooperation. The partners in this system have established technical standards and norms for influenza surveillance and diagnosis and have enabled millions of doses of vaccines to be produced and administered. While GISN continues to protect the world's population from epidemics of seasonal human influenza, it is now also helping countries around the world respond to the H5N1 threat and prepare for the next influenza pandemic. ■

The opinions expressed in this article do not necessarily reflect the views or policies of the U.S. government.