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I. Objectives of Human Surveillance

Surveillance for influenza requires global and national monitoring for both virus and disease activity. Influenza surveillance has three primary objectives:

Surveillance Objectives

1. To determine when, where, and which influenza viruses are circulating in the U.S. and globally;
2. To determine the intensity and impact of influenza activity on defined health outcomes and to identify unusual or severe outbreaks; and
3. To detect the emergence of novel influenza viruses that may cause a pandemic

Identifying circulating strains and novel virus strains is important for annual vaccine preparation, assisting health-care providers in making treatment decisions, and pandemic detection. Disease surveillance is necessary because influenza virus infections can lead to very large numbers of illnesses, hospitalizations and deaths and information on impact is needed to guide resource planning and prevention and control efforts.

In a pandemic, surveillance data will provide important information on the spread of disease globally and to communities in the U.S. guiding local implementation of control measures that may include travel restrictions, closing schools and canceling public gatherings, and initiating antiviral chemoprophylaxis in defined target groups. Surveillance data, supplemented by special studies, will provide information on the epidemiology of the pandemic that will help decision-makers determine what control strategies may be effective and to re-evaluate recommended priority groups for vaccination and antiviral therapy. Surveillance for antiviral resistance among influenza isolates will help guide use of antiviral chemoprophylaxis and therapy.

II. Global Surveillance

Building international capacity for influenza surveillance has been a global priority. In 1948, the World Health Organization (WHO) established an international laboratory-based surveillance network for influenza. The network currently consists of 112 national influenza center (NIC) laboratories in 83 countries and four WHO Collaborating Centers, one of which is located in the Influenza Branch of the U.S. Centers for Disease Control and Prevention (CDC). The primary purposes of the WHO network are to detect the emergence and spread of new antigenic variants of influenza in order to update the formulation of annual influenza vaccines in a timely manner; to assemble and disseminate information about global influenza activity; and to detect novel influenza strains (i.e., influenza A subtypes that have not recently circulated among people) that infect humans leading to the implementation of control measures and providing early warning of a possible pandemic.

The WHO Collaborating Center for Epidemiology, Surveillance, and Control of Influenza located at CDC annually produces and distributes worldwide the WHO influenza reagent kits needed to identify the influenza viruses that are expected to circulate. This Center also conducts comparative serologic and molecular studies of representative and unusual influenza viruses sent from NICs around the world. Results of these studies are provided to a large number of end users, including the four international Collaborating Centers (Australia, Japan, United Kingdom and U.S.), WHO headquarters, the originating national laboratories, and the Food and Drug Administration's Vaccine and Related Biological Products Advisory Committee, which annually recommends influenza vaccine strains for use in the United States.

As a result of recent avian influenza outbreaks and because of SARS enhancements to the global influenza system include heightened and more rapid communication, collaboration and sharing of data and specimens among laboratories and public health entities. However, global surveillance capacity is still of major concern. The Asian poultry and human outbreaks caused by highly pathogenic avian influenza A (H5N1) viruses in 2003 and 2004 have highlighted several important gaps that prevent our ability to rapidly identify avian influenza viruses with pandemic potential. These include:

- Conspicuous geographic gaps in human influenza surveillance
- Limitations in information, laboratory and epidemiologic training and technology transfer for rapid identification and analysis of avian influenza viruses in many affected countries
- Obstacles to sharing of information, resources and specimens among agriculture and human health authorities

Many countries in the world do not have adequate staffing, resources or training to conduct timely influenza surveillance. Efforts are underway to strengthen international influenza surveillance starting in Asia. To accomplish this goal, a variety of mechanisms use a regional strategy and build on existing infrastructure, programs and the WHO global influenza surveillance system. Mechanisms will range from bilateral support for development of in-country influenza surveillance networks, strategic placement of staff within countries and leveraging collaboration with other government partnerships. Other efforts to further the WHO global agenda to increase information on the impact and burden of disease caused by influenza will facilitate a better understanding of the need to conduct influenza surveillance, formulate vaccine policy and stimulate vaccine production in new countries globally are also important.

III. U.S. Surveillance

In addition to its international role, CDC also conducts and coordinates influenza surveillance in the United States. Surveillance foci include collecting influenza viral isolates for testing, monitoring morbidity and mortality, and identifying unusual or severe influenza outbreaks. The U.S. national influenza surveillance system consists of four components (*see Table 1*): laboratory surveillance, outpatient influenza-like illness (ILI) surveillance, pneumonia and influenza (P&I) related mortality surveillance, and an assessment of influenza activity at the state level. Traditionally, U.S. influenza surveillance has been conducted from October through mid-May but is now being conducted year-round. Year-round influenza surveillance will provide information on the baseline level of influenza activity during the summer. These data have the potential to become an important component of early detection for a pandemic.

Table 1: Summary of US Influenza Surveillance System

Surveillance Objective	Existing Infrastructure	Data Elements
Determine when, where, and which influenza viruses are circulating	**WHO and National Respiratory and Enteric Virus Surveillance System Collaborating laboratories:** a network of state and local public health labs, hospital labs and commercial labs that test specimens collected as a part of routine patient care, targeted surveillance, and outbreak investigations	Weekly reports of: ▪ # of specimens tested ▪ # positive for influenza by type/subtype Labs send a subset of influenza isolates to CDC for further testing
Determine the impact of influenza on outpatient morbidity	**U.S. Influenza Sentinel Provider Surveillance Network**: a collaborative effort between CDC, state health departments, and primary health care providers	Weekly reports of: ▪ # of patients with ILI by age ▪ # of patients seen for any reason Providers collect respiratory specimens from a subset of ILI patients for influenza testing at the state laboratory
Determine the impact of influenza on mortality	**122 Cities Mortality Reporting System:** vital statistics offices of 122 U.S. cities	Weekly reports of: ▪ # of death certificates with influenza or pneumonia as underlying or contributing cause of death ▪ Total # of death certificates filed
Influenza activity at the state level	**State and Territorial Epidemiologists Report:** State health departments report the overall level of influenza activity in the state	Weekly reports of influenza activity: ▪ None; ▪ Sporadic; ▪ Local; ▪ Regional; or ▪ Widespread

Influenza surveillance data are used by national, state, and local public health officials, healthcare practitioners, policy makers, the general public, and the media to inform vaccine strain selection, make healthcare decisions, and develop policy. State health department officials have access to surveillance data in real time on a password protected website and can use these data to inform local decisions and follow-up unusual events. From October through mid-May,

CDC produces a weekly surveillance report consisting of national and regional level data that is widely disseminated nationally, to interested colleagues internationally, and is available to the general public in a variety of ways including the Internet (http://www.cdc.gov/flu/weekly/fluactivity.htm). Periodically throughout the year, more detailed descriptions of influenza activity and issues related to influenza prevention and control are published in CDC's Morbidity and Mortality Weekly Report. Additional details on each of the components of influenza surveillance in the U.S. are provided below.

CDC supports enhanced influenza surveillance activities through the Epidemiology and Laboratory Capacity (ELC) Grants that were established in 1997. Funding distributed to state and local influenza programs through the ELC cooperative agreement has steadily increased from the first awards in 1997 with a small amount of funding to five states totaling under $100,000 dollars through the present time with approximately 47 states or major metropolitan areas funded more than $2,000,000. States and cities receiving Influenza ELC-influenza funding are encouraged to achieve three highlighted influenza epidemiology and laboratory surveillance capacities: sentinel physician surveillance, viral isolation and subtyping, and year round surveillance. Each state targeted funding to meet one or more of these three priorities and used funding for support of improvements that included the assignment or hiring of an Influenza Coordinator, recruitment of sentinel physicians to collect influenza specimens and report influenza-like illness to the state, laboratory infrastructure enhancements to increase influenza testing capabilities and/or expansion of influenza surveillance activities to year-round. ELC grants have been instrumental in building U.S. influenza surveillance over the past years and could enable further improvements if funding were increased.

A. Virologic Surveillance

In the United States, surveillance for influenza viruses is conducted through a combined network of approximately 120 WHO and National Respiratory and Enteric Virus Surveillance System (NREVSS) collaborating laboratories. Each week, participating laboratories report to CDC the total number of specimens received by the laboratory for respiratory virus testing and the number of specimens positive for influenza A (H1), A (H3N2), A (not subtyped), or B. The preferred testing method is viral culture; however, both culture and antigen detection results can be reported as long as the test used can identify both influenza A and B and distinguish between the two.

While the WHO and NREVSS laboratory systems are similar, they differ in several ways. The U.S. WHO Collaborating Laboratories System consists of laboratories in state or local health departments, universities, large tertiary care hospitals, and the Department of Defense. All state health departments with the ability to test for influenza participate in this network. In addition to reporting the data elements outlined above, these laboratories also report their results by age group and submit weekly reports to CDC either by fax, electronically through the Public Health Laboratory Information System (PHLIS) or via a password protected, editable, internet reporting system piloted during the 2003-04 influenza season.

Each year, CDC's Influenza Branch provides all the WHO collaborating laboratories with an

influenza reagent kit free of charge. This kit contains reagents for the identification, typing and subtyping of influenza isolates. These laboratories are requested to submit a subset of their isolates to the CDC Influenza Branch Strain Surveillance Laboratory for detailed antigenic characterization and possible genetic characterization.

Any clinical diagnostic virology laboratory in the U.S. is eligible to participate in the NREVSS if it routinely tests specimens for any of the following agents: respiratory syncytial virus, human parainfluenza viruses, adenoviruses, influenza virus, or rotavirus. Typically, laboratories in the NREVSS system are hospital or commercial laboratories. These laboratories report the data elements described above but do not break down their data by age and are less likely to report influenza A virus subtype information. Reports through the NREVSS system can be submitted via a telephone or Internet reporting system, or by fax.

The approximately 120 WHO and NREVSS laboratories tested approximately 100,000 patient samples and reported between 10,000 and 16,000 positive tests each year from 1997 - 2003. At least one WHO or NREVSS laboratory is located in each state. A subset isolates are submitted to CDC each year for antigenic analysis and a further subset of these go on for genetic analysis.

There are two classes of antiviral drugs that are effective against influenza viruses, the adamantanes (amantadine and rimatadine) and neuraminidase inhibitors (oseltamivir and zanamivir). Testing for antiviral resistance against adamantanes is performed on specimens in which the likelihood of resistance is increased and testing is requested. An example of such a situation is an institutional outbreak of influenza in which adamantanes are used both for treatment and prophylaxis to control the outbreak. Through the Neuraminidase Inhibitor Susceptibility Network (NISN) CDC tests a large subset of the isolates submitted for antigenic characterization for resistance to neuraminidase inhibitors.

From 1992 to 1997, CDC's Influenza Branch performed national and international surveillance for influenza A viruses resistant to amantadine and rimantadine. This project was terminated in 1997 to provide resources to investigate the outbreak of avian influenza A (H5N1) in Hong Kong, but has recently been re-established. Studies on avian influenza viruses of different subtypes have been expanded to improve pandemic preparedness including surveillance for NI resistance in field isolates collected from around the world. In addition, detailed genetic analyses of resistant viruses will be conducted. *In vitro* selection strategies to identify genetic mutations that correlate with resistance and a small-animal model to evaluate *in vivo* the resistance and transmissibility of NI resistant influenza viruses are being developed. A reverese genetics system in which viruses with specific mutations associated with drug resistant phenotypes will evaluate the role of these mutations on antiviral drug resistance. Finally, development of protocols for new molecular methods, such as real-time RT-PCR, for more rapid diagnosis of drug-resistance variants among human and avian influenza virus isolates will be carried out. Detailed protocols for these assays will be prepared and be available to transfer to state and national partners by the end of the project.

B. Outpatient Influenza-like Illness Surveillance

Outpatient data on influenza-like illness (ILI) are collected through the U.S. Influenza Sentinel Provider Surveillance Network, a collaborative effort between CDC, state and local health departments, and health care providers. This effort began in 1997 and the system has grown significantly since that time. During the 2003-04 season, approximately 1,100 providers in all 50 states regularly reported weekly data to CDC.

Participating physicians identify clinical illness cases consistent with influenza (i.e., fever ≥100°F AND cough and/or sore throat in the absence of a known cause other than influenza) among patients who make medical care visits for any reason. Sentinel providers submit weekly reports of the number of patient visits for any reason each week and the number of patient visits for ILI by age group (0-4, 5-24, 25-64, ≥65 years). From these data, the percent of patient visits for ILI are calculated on a national, regional, and state level.

Sentinel providers transmit data to a central data repository at CDC on a weekly basis. The majority of providers report via the Internet making the data immediately available to CDC, the state health department, and the provider. There is a dedicated, password protected website (http://www2.ncid.cdc.gov/flu/) for the U.S. Influenza Sentinel Provider program that allows different levels of access for data entry and viewing by the state health departments and providers (e.g. states can enter and view data for all providers in their state, while providers can enter and view data for their site only). Reporting via a telephone reporting system and fax are available to enable participation by sites without internet access and to serve as backup systems in the event of technical problems. This data is uploaded to the website each morning Monday-Friday.

CDC recommends that sentinel providers have the option of submitting a throat or nasopharyngeal swab specimen from a subset of ILI cases for virologic testing at the state laboratory at no charge to the provider. CDC maintains a contract lab for testing of sentinel provider specimens from those states whose laboratory cannot test for influenza. The subset of patients tested should be those of particular surveillance interest, especially a few at the beginning, peak, and end of the season; during the summer; all unusual clinical cases or unusually severe cases; and outbreak-related cases. This service provides valuable information for local providers and public health officials that influenza has entered their community but it should not be relied upon for individual case diagnosis.

The sentinel provider surveillance network has grown from 214 sites reporting 523,588 patient visits during the 1996-1997 influenza season, to approximately 1,600 sites reporting more than 7 million patient encounters for 2002-03. This increased volume of data and improved geographic distribution of surveillance sites increases the potential for earlier detection of outbreaks of influenza-like illness in smaller geographic areas. The potential usefulness of applying a CDC-developed outbreak detection system, the Early Aberration Reporting System, to analyze weekly ILI data by state and age group is being explored. Based on preliminary analyses, this may be a valuable tool for detection of state-level increases in ILI, but the methodology needs to be further evaluated and refined.

C. Influenza-Related Mortality Surveillance

The 122 Cities Mortality Reporting System allows for a rapid assessment of deaths that may be influenza-related. Each week throughout the year the vital statistics offices of 122 U.S. cities report the total number of death certificates filed for that week and the number of deaths for which pneumonia or influenza was mentioned anywhere on the certificate. The number of deaths reported through this system represents a sample of between 1/4 and 1/3 of all deaths occurring in the U.S.

A robust regression procedure run on the previous five years of data is used to calculate a seasonal baseline. If the proportion of pneumonia and influenza (P&I) deaths for a given week exceeds the baseline value for that week by a statistically significant amount, then P&I deaths are said to be above the epidemic threshold, and the proportion of deaths above threshold are considered attributable to influenza. On a weekly basis, data from all 122 cities are combined, and the percent of all deaths due to P&I are calculated and compared to the percent that was expected for that week. Data from the 122 Cities System can be analyzed by age group and geographic region; however, interpretation of that data requires the development of a separate baseline for each data subset. It is not valid to compare data from a particular city or region to the national baseline.

The 122 Cities Mortality Reporting System is not designed to estimate the total number of influenza related deaths in the U.S. The majority of P&I deaths counted through the system are included because pneumonia, not influenza, is listed on the death certificate. Pneumonia deaths occur throughout the year and the number increases during winter months even if influenza virus is not circulating. In addition, while many influenza related deaths are due to secondary bacterial pneumonia, some persons who die from influenza will not have pneumonia or influenza coded on the death certificate as a contributing cause. The 122 cities system is designed only to tell when the proportion of deaths with pneumonia or influenza listed on the death certificate are above what would be expected for that week if influenza viruses were not circulating.

D. State and Territorial Epidemiologist's Report

The State and Territorial Epidemiologist's Report consists of a weekly report from each state epidemiologist (or their designee) of the overall level of influenza activity in the state. This system provides the only state level influenza data that CDC makes publicly available and these data are widely used by the media, the public, and public health officials. All 50 states, New York City, and Washington DC, report the level of influenza activity for their state/city to CDC each week between October and mid-May. Disease activity is classified into one of five categories based on specific definitions (*see Table 2*).

Table 2: Influenza Activity Levels

Activity Level	ILI activity*/Outbreaks		Laboratory data
No activity	Low	**And**	No lab confirmed cases†
Sporadic	Not increased	**And**	Isolated lab-confirmed cases
	OR		
	Not increased	**And**	Lab confirmed outbreak in one institution‡
Local	Increased ILI in 1 region**; ILI activity in other regions is not increased	**And**	Recent (within the past 3 weeks) lab evidence of influenza in region with increased ILI
	OR		
	2 or more institutional outbreaks (ILI or lab confirmed) in 1 region; ILI activity in other regions is not increased	**And**	Recent (within the past 3 weeks) lab evidence of influenza in region with the outbreaks; virus activity is no greater than sporadic in other regions
Regional (doesn't apply to states with ≤4 regions)	Increased ILI in ≥2 but less than half of the regions	**And**	Recent (within the past 3 weeks) lab confirmed influenza in the affected regions
	OR		
	Institutional outbreaks (ILI or lab confirmed) in ≥2 & less than half of the regions	**And**	Recent (within the past 3 weeks) lab confirmed influenza in the affected regions
Widespread	Increased ILI and/or institutional outbreaks (ILI or lab confirmed) in at least half of the regions	**And**	Recent (within the past 3 weeks) lab confirmed influenza in the state.

* ILI activity can be assessed using a variety of data sources including sentinel providers, school/workplace absenteeism, and other syndromic surveillance systems that monitor influenza-like illness.

† Lab confirmed case = case confirmed by rapid diagnostic test, antigen detection, culture, or PCR. Care should be given when relying on results of point of care rapid diagnostic test kits during times when influenza is not circulating widely. The sensitivity and specificity of these tests vary and the predicative value positive may be low outside the time of peak influenza activity. Therefore, a state may wish to obtain laboratory confirmation of influenza by testing methods other than point of care rapid tests for reporting the first laboratory confirmed case of influenza of the season.

‡ Institution includes nursing home, hospital, prison, school, etc.

**Region: population under surveillance in a defined geographical subdivision of a state. A region could be comprised of 1 or more counties and would be based on each state's specific circumstances. Depending on the size of the state, the number of regions could range from 2 to approximately 12. The definition of regions would be left to the state but existing state health districts could be used in many states. Allowing states to define regions would avoid

somewhat arbitrary county lines and allow states to make divisions that make sense based on geographic population clusters. Focusing on regions larger than counties would also improve the likelihood that data needed for estimating activity would be available.

E. Surveillance Challenges and Enhancements

Although the current influenza surveillance system achieves the objectives of monitoring influenza viral strains, morbidity and mortality, and identifying outbreaks, interpreting surveillance data poses several challenges. Because most cases of influenza are not identified etiologically (i.e., not confirmed as influenza by a laboratory test) it is impossible to specifically count influenza cases, hospitalizations and deaths. Laboratory testing of all ILI cases would be prohibitively expensive and time consuming given the large number of such cases that occur each year. And because infections other than influenza can cause ILI, accurate counts of influenza cases cannot be determined based on the frequency of a clinical syndrome. Finally, many persons infected with influenza do not seek medical care and therefore remain unidentified. For these reasons, influenza activity is measured indirectly by determining a proportion of (1) specimens tested that are positive for influenza, (2) healthcare provider visits for ILI, and (3) deaths due to pneumonia or influenza, and comparing these proportions with a baseline level of expected activity.

An additional challenge for monitoring the effect of influenza viruses on hospitalization or mortality is that many severe influenza-related illnesses or deaths are due to secondary bacterial infections (most commonly bacterial pneumonia) or worsening of chronic diseases. Because surveillance data have not been able to capture all influenza-related hospitalizations and deaths, and because the P&I category also includes many persons who do not have influenza, estimating the burden of influenza requires conducting specific studies and using mathematical modeling. These studies evaluate differences in health outcomes, death or hospitalization, during the influenza season and time periods before and after influenza season for defined diagnostic codes. Excess P&I mortality or hospitalizations typically have been evaluated but underestimate the impact of influenza by omitting deaths related to worsening of a chronic condition, such as congestive heart failure, following an influenza infection. By contrast, analyzing seasonal differences in all causes of mortality would likely over-estimate the role of influenza in excess winter mortality. In 2003, an analysis by CDC introduced an intermediate measure that may best reflect influenza-related mortality: excess respiratory and circulatory deaths. Respiratory and circulatory deaths are a more sensitive estimate of the impact of influenza on mortality than pneumonia and influenza deaths alone and are more specific than all causes of death, therefore, providing a more accurate estimate of deaths attributable to influenza.

Several activities to enhance influenza surveillance currently are underway:

- The ability of public health laboratories to identify influenza from clinical specimens is being enhanced through the distribution of standardized protocols for lab methods, by introducing new techniques, such as multiplex PCR and by expanding the role for use of molecular techniques to rapidly diagnose respiratory agents including influenza types and subtypes. CDC, in collaboration with the Association of Public Health Laboratories, has planned and will be conducting training for state public health laboratory personnel in

order to promote standard molecular techniques for the identification of influenza virus types and subtypes including those normally circulating in human populations, H1 and H3 and recent avian subtypes of interest, H5 and H7. The incorporation of these data into the surveillance reporting system will increase information on the circulation of influenza viruses and help develop a better understanding of the impact of specific viral subtypes.

- Studies have documented that children are major contributors to the spread of influenza within the community. In addition, there is increasing awareness that influenza is associated with significant morbidity and mortality among children. In order to better understand the dynamics of influenza in children, pediatric influenza-associated deaths have recently been added to the national reportable disease list. Implementation of this surveillance will aid in the identification of high-risk groups and in formulating improved immunization policies.

- In three metropolitan areas included in the New Vaccine Surveillance Network, active-surveillance is ongoing to detect all influenza cases among children less than 5 years old who are admitted to hospital. Key features of this system are that it includes all hospitals that admit children from the surveillance counties; laboratory testing is done to detect which children admitted with febrile or respiratory illness actually have influenza; and data are being collected to characterize the clinical and epidemiological features of influenza in children. Based on influenza cases detected in children, studies are being done to evaluate the effectiveness of influenza vaccination and the costs associated with pediatric influenza illness.

- In nine Emerging Infections Program network sites, an investigation to characterize the burden of severe, laboratory-confirmed pediatric influenza in the U.S. was initiated during the 2003-2004 influenza season. Specific objectives include: 1) determining the age-specific rates of laboratory confirmed influenza-associated hospitalization among children aged <18 years in the surveillance areas during the 2003-2004 influenza season; 2) determining the rate of serious influenza-associated complications, such as secondary bacterial infections and the need for ICU admission/mechanical ventilation; and 3) describing clinical and epidemiologic characteristics of pediatric case-patients requiring hospitalization for influenza infection. Ongoing surveillance for severe influenza infections in children in the EIP sites is planned.

- Efforts continue to increase the number of regularly reporting sentinel provider sites in each state to 1 per 250,000 population or at least 10 in states with small population.

- Efforts to develop studies to obtain annual estimates of vaccine effectiveness against laboratory confirmed influenza illness are underway. Case-control studies in adult, and possibly pediatric populations, are being established and vaccine effectiveness estimates for laboratory confirmed disease will be reported to CDC on an ongoing basis during the study, with final results at the end of each influenza season.

- Collaborations are being established with several Asian countries to strengthen laboratory capacity and influenza surveillance in humans and animals as part of the Global Disease Detection initiative.

HHS has been working with other Asian partners in enhancing the region's ability to detect and respond to outbreaks of influenza. HHS, in cooperation with the Department of Agriculture sent teams to assist WHO in Vietnam and Malaysia. Through field staff in Vietnam and Thailand, we provided assistance to the governments in affected countries. The WHO Collaborating Centre for Reference and Research on Influenza served as a resource for countries around the world seeking to verify and characterize influenza outbreaks in their countries. HHS, through the International Emerging Infections Program (IEIP) in Bangkok, Thailand, assisted the Thai Ministry of Public Health in responding to the avian influenza outbreak earlier this year. Finally, the HHS representative in Vietnam and a USDA representative played a central role in discussions with the WHO, the Food and Agriculture Organization, and the Vietnamese Government in monitoring and assisting in the response to the influenza outbreak

At the Leaders' meeting of the Asia-Pacific Economic Cooperation (APEC) October 2003, President George W. Bush announced a partnership with the Government of Singapore to establish the Regional Emerging Diseases Intervention (REDI) Center to be based in Singapore. This innovative partnership will serve as a regional base of operations for U.S.-based HHS staff involved in emerging and re-emerging infectious disease research and surveillance. Through the REDI Center, HHS hopes to provide training to health professionals throughout the region in research and disease surveillance and link together regional experts who can rapidly respond to outbreaks of an unusual nature.

Additionally, also through APEC, the U.S. has taken the lead in calling for and organizing the APEC Health Task Force. This new group within APEC is designed to respond to the need for a more efficient and effective mechanism to address health issues in APEC. The SARS and avian influenza epidemics have awakened the member economies to the large impacts of health on trade, tourism and economic development and thus have pledged to work together more effectively. HHS is pleased to provide the first chair to this group.

IV. Surveillance by Pandemic Phase

Surveillance needs will expand and change when an influenza pandemic could be imminent – for example, when a novel influenza strain is identified in one or more people – and when a pandemic actually occurs. Needs will differ depending on where disease has been identified; whether there is coexisting disease among poultry or other animals; whether transmission occurs between people and its efficiency; and whether disease outbreaks have occurred in the U.S. or other countries. In addition to increased data collection needs, there will be increased demands for surveillance information as many more people and organizations will be interested in influenza and requests for more types of data will be made on a more frequent basis. The best way to prepare for these increased demands are to strengthen surveillance systems before a pandemic occurs and to anticipate and plan for them.

A. The inter-pandemic period *(WHO Phase 0, Level 0)*

The essential requirement for effective national and state pandemic surveillance is a well-functioning inter-pandemic system. Performance benchmarks for such a system include:

- A state public health laboratory that isolates and subtypes influenza viruses during the influenza season, maintains the capability to isolate and subtype influenza viruses year-round, and that reports these data weekly to CDC year-round.
- A state public health laboratory that continues to receive clinical specimens and perform viral culture in the face of increasing usage of rapid influenza diagnostic tests and PCR testing.
- A state public health laboratory that is (or is working towards) transmitting their influenza surveillance data electronically to CDC via the Public Health Laboratory Information System (PHLIS).
- An influenza sentinel provider program that includes at least the minimum number of health care providers (1/250,000 persons or a minimum of 10 providers in states with smaller populations) who regularly report their weekly data to CDC via the Internet year-round.
- An active state influenza surveillance coordinator who:
    - Monitors sentinel provider data weekly for completeness and/or errors;
    - Provides feedback and maintains contact with sentinel providers weekly to encourage reporting and follow-up on unusual reports;
    - Contributes to state pandemic planning activities;
    - Establishes and maintains strong working relationships with the state laboratory;
    - Encourages sentinel providers to submit specimens for viral culture to the state laboratory.
- Weekly assessment of overall influenza activity level (none, sporadic, local, regional, widespread) in the state and timely reporting of that data to CDC.

In addition to established capabilities, state health departments, as part of their pandemic influenza preparedness and response planning process should have a written contingency plan for enhancing virologic and disease-based surveillance systems in the event of a novel virus or pandemic alert and a pandemic. Plans should address coordination between public health, hospital and other private laboratories to respond to increased demands for testing; assuring laboratory surge capacity; safety for laboratory workers in the context of an increased workload and potential handling of highly pathogenic viruses; and rapid ability to report results to local, state, and national levels.

States also should develop strategies to monitor influenza-related deaths and hospitalizations. Approaches may include the use of existing databases or development of new systems such as daily fax or telephone reporting of hospital admissions for influenza like illness and deaths identified in hospitals or the community.

B. Novel virus alert (*WHO Phase 0, Level 1, Level 2)*

Human infection caused by a novel influenza virus may be identified first in the U.S. but is more likely to initially occur in another country. CDC will be informed of a case as part of the global

surveillance network and will contribute to international surveillance by characterizing viral isolates, supplying reagents for strain identification, and providing technical assistance. When a novel virus alert occurs, states should enhance influenza surveillance activities by:

- Increasing case detection among persons who recently traveled to the outbreak area and present with clinical illness possibly caused by influenza including pneumonia, acute respiratory distress syndrome, or other severe respiratory illness. Appropriate specimens should be collected to diagnose influenza infection. In some situations, if the novel influenza virus is a highly pathogenic avian strain, such as with the 2004 H5N1 influenza virus in Asia, local hospital laboratories should not attempt viral isolation because of the potential risk that the strain could spread. Specimens should be sent to the state public health laboratory or to CDC where isolation and subtyping can be done under more stringent biocontainment conditions. Influenza infection can be diagnosed locally using antigen detection, immunofluorescence, or PCR. Guidance will be provided by CDC appropriate to each specific novel virus alert.

- Ensuring that all components of surveillance are operational regardless of the time of year and that all participating laboratories and sentinel providers are reporting data to CDC each week.

- Subtyping all influenza A viruses identified in clinical specimens and, as always, reporting any influenza A virus that cannot be subtyped to CDC immediately. CDC will provide instructions on the safe handling of a potential novel influenza virus.

- Obtaining reagents and protocols from CDC (when they become available) to detect and identify the novel strain.

- Recruiting and enrolling additional sentinel providers, if necessary, to reach the minimum of one regularly reporting provider for every 250,000 person (minimum of 10 in states with smaller populations).
- Monitoring and instituting recommendations from CDC for any additional surveillance activities that should be undertaken given the specific circumstances. For example, in response to the identification of human influenza A (H5N1) cases in Vietnam and Thailand in 2004, CDC asked states to work with hospitals to obtain samples for influenza virus testing on all patients who: (1) were hospitalized with unexplained pneumonia, acute respiratory distress syndrome (ARDS), or severe respiratory illness and (2) who had traveled to Asia within 10 days from onset of symptoms; or from less severely ill patients who had had contact with poultry in an affected country. Because viral culture of influenza A(H5N1) viruses requires biosafety level 3+ facilities, CDC recommended PCR methods be used for initial testing at state health departments and all influenza A positive samples and samples from states without PCR testing capability be sent to CDC for further testing.
- Reviewing contingency plans for further enhancing influenza surveillance if efficient person-to-person transmission of the novel virus is confirmed.

CDC will participate in the investigation of early international cases of infection with a new virus to determine characterize the epidemiology of the novel virus and conduct thorough investigations of all early cases either originating in the U.S. or imported into the country.

C. Pandemic Alert *(WHO Phase 0, Level 3)*

The surveillance implications of documenting efficient person-to-person transmission of a novel influenza virus and of outbreaks in one or more countries may differ depending on where disease has occurred. The most important role of surveillance during this phase is to identify whether the novel influenza strain causes infection in the surveillance area, leading to implementation of outbreak control and other response activities. Key surveillance enhancements at this phase include:

- Assessing the need to screen travelers arriving in the U.S. from affected countries.
- Investigating the epidemiology of all early cases either originating in the U.S. or that are imported into the country.
- Increasing laboratory diagnosis of influenza, including through use of rapid antigen detection tests, for persons with compatible clinical syndromes, particularly among those who may have had recent exposure at the site of an outbreak. Laboratories should institute plans for testing substantially more specimens than usual. CDC will provide guidelines to assist with triage of specimens for testing and for choosing which isolates to send to CDC.
- Reporting test results daily to CDC. The completeness and timeliness of reports from all participating laboratories and sentinel providers should be assessed and non-reporters should be contacted to improve their performance as necessary.
- Investigating outbreaks and increases in ILI, including those detected through the sentinel provider surveillance system.

D. Confirmation of the onset of a pandemic until the end of pandemic disease *(WHO Phases 1 to 4)*

As pandemic disease occurs in the U.S., surveillance priorities will include detecting when the pandemic strain first causes disease in a community so that control measures, such as chemoprophylaxis, can be initiated; and monitoring the epidemiology and impacts of the pandemic. In the 1918 pandemic, the severity of disease increased between successive pandemic waves illustrating the importance of ongoing monitoring of disease and health outcomes. Influenza viruses also may develop resistance to antiviral agents, particularly to amantadine and rimantadine if used inappropriately.. Thus, monitoring for resistance can help guide antiviral use recommendations. In addition to continuing the enhanced surveillance described for earlier pandemic phases, activities should include:

- Enhanced monitoring for antiviral resistance.
- Ensuring that studies are in place to monitor vaccine effectiveness
- Monitoring health impacts including deaths and hospitalizations. Community impacts could be assessed by measuring absenteeism in key industries or sectors.

- During the period between pandemic waves (*Phase 3*) and after the pandemic (*Phase 5*), the quality of surveillance should be assessed and recommendations made for improvement.

V. Surveillance System Enhancements and Next Steps

Although U.S. and global influenza surveillance have improved in recent years, further enhancements can strengthen the ability of the system to detect the emergence and spread of novel influenza strains. Given the proper resources, these include:

- Epidemiology and laboratory capacity building globally
- Enhanced collaboration with agricultural authorities and studies to better understand the interface between human and animal disease
- Development of global guidelines for performing influenza surveillance in a variety of resource settings.
- Development of enhanced electronic reporting for all components of the influenza surveillance system including electronic mortality reporting.
- Development of new diagnostic techniques such as microchips, new rapid tests, new screening methods of antiviral resistance and improved PCR techniques
- Laboratory automation to increase the throughput and processing of more specimens will enhance our ability to gather and analyze more surveillance data

VI. Veterinary surveillance

No organized WHO program currently exists to support global surveillance in animals, and animal influenza surveillance abroad is extremely variable from country to country, depending on national priorities, the economic importance of animal influenza, and the infrastructure available to support such activities. WHO has initiated limited systematic influenza surveillance in swine and recent avian outbreaks caused by highly pathogenic influenza strains are likely to lead to new avian surveillance activities. In response to the first known transmission of highly pathogenic avian influenza viruses from birds to man in 1997, NIH has supported an animal influenza surveillance program in Hong Kong and plans to expand coverage into mainland China and other parts of Asia. The Office International des Epizooties (OIE) has established reference laboratories for avian and equine influenza. These laboratories provide diagnostic testing including virus characterization, reagents, and training. The OIE member countries report outbreaks of avian, equine and swine influenza, and the OIE prepares a yearly summary of these reports. Additionally, the UN Food and Agriculture Organization (FAO) decided to establish a veterinary surveillance network in Southeast Asia, which will build on an existing effort to begin limited systematic influenza surveillance in swine (www.fao.org).

The U.S. Department of Agriculture (USDA) conducts influenza surveillance in domestic animals. Coordination with USDA is important because a pandemic strain is likely to arise from reassortment of animal and human influenza viruses. Recent outbreaks in domestic poultry in Asia and Europe associated with cases of human disease highlight the importance of coordinating surveillance activities. Surveillance for influenza A viruses in poultry in the U.S. has increased substantially since the outbreak of highly pathogenic avian influenza (HPAI) in

Pennsylvania and surrounding states in 1983 and 1984. Individual states are generally responsible for the development and implementation of surveillance programs that are consistent with the size and complexity of the resident poultry industry. Although there is considerable variation among states regarding the number and source of samples tested, the samples are derived from a wide range of sources, one of which is the investigation of suspected cases of avian influenza. Investigations may be conducted by state animal health officials, USDA-accredited veterinarians, university personnel, or members of the poultry industry. Samples from affected flocks are routinely submitted to state laboratories for diagnosis. If importation of HPAI is suspected, a Foreign Animal Disease Diagnostician will conduct an investigation and submit samples directly to the National Veterinary Services Laboratories (NVSL) in Ames, Iowa.

Other sources of surveillance samples from poultry come from monitoring for serum and egg yolk antibodies at processing plants, routine testing of game birds, qualifying birds for export, and testing ratites (flightless birds) prior to interstate movement. In addition, the USDA's Animal and Plant Health Inspection Service (APHIS) has been monitoring live bird markets in the northeastern region of the U.S. since 1986 for the presence of avian influenza viruses that may pose a threat to commercial poultry.

There is currently a ban on importing ratites and hatching eggs of ratites from Cambodia, Indonesia, Japan, Laos, Pakistan, Peoples' Republic of China, South Korea, Thailand, Vietnam and British Columbia, Canada. Birds submitted for entry into the United States from countries and areas not included in the ban must be quarantined in USDA approved quarantine facilities. During quarantine, avian influenza virus isolation is attempted on samples collected from all dead birds and some live birds. Any AI virus isolated is characterized and if HPAI is isolated the birds kept out of the country.

Reagents for serologic monitoring for avian influenza are provided free of charge by the NVSL. In addition, suspected isolates of avian influenza and samples positive for influenza antibodies may be submitted to the NVSL for confirmation, subtype identification, and assessment of pathogenicity. Documented outbreaks and infections are reported each year in the Proceedings of the U.S. Animal Health Association Annual Meeting.

Several programs exist for surveillance in wild birds in North America. NIH supports annual surveillance of influenza viruses in wild migrating birds in North America. Collaborations exist with the Canadian Wildlife Service to isolate influenza viruses from migratory birds. Results obtained after analysis of the virus isolates from wild birds are published periodically.

Surveillance in the U.S. for influenza A viruses in swine and horses is considerably less systematic than in poultry. While no requirement exists for USDA notification when cases or outbreaks of influenza occur in these animals, considerable interest exists in understanding the viruses that are circulating among them. It is clearly recognized that swine influenza viruses are endemic in pigs in the U.S. and that outbreaks may occur each year. In general, only outbreaks in swine of unusual severity or duration are likely to be investigated and reported. On the other hand, surveillance for influenza viruses causing disease in horses has practical utility because data generated from analysis of equine influenza viruses can be used to guide equine influenza vaccine formulation. The Animal Health Trust, Newmarket, U.K. has taken the lead in

organizing a program for equine influenza surveillance and reporting, primarily in Europe and the United States. Based on this surveillance an annual report is published (http://www.aht.org.uk).