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Seasonal and pandemic influenza surveillance*Lynnette Brammer, Alicia Postema & Nancy Cox***Introduction**

Influenza viruses belong to the Orthomyxoviridae family and are divided into types A, B, and C. Influenza type A and B viruses are responsible for epidemics of respiratory illness that occur every winter in temperate climates and year-round in the tropics. Influenza type C virus produces a milder infection, does not cause epidemics, and will not be discussed further in this chapter. Influenza type A viruses are divided into subtypes based on surface proteins called hemagglutinin (HA) and neuraminidase (NA). To date, 16 HA subtypes and nine NA subtypes have been identified. However, in the twentieth century, influenza viruses bearing only three HA (H1, H2, and H3) and two NA subtypes (N1 and N2) have circulated widely in humans. Influenza viruses are notable for their ability to change through two different mechanisms: antigenic drift and antigenic shift. Antigenic drift is the slow, continuous change affecting both influenza type A and B viruses that allows for multiple infections of an individual over their lifetime and requires frequent updating of the viral components of trivalent influenza vaccine. Antigenic shift is an infrequent but dramatic change, occurring only among influenza type A viruses, that results in a new influenza A subtype to which most or all of the population has no immunity. If the new virus can infect humans and transmit easily from person to person, a pandemic may occur.

The burden of influenza in nonindustrialized countries is not well defined. However, during annual epidemics in industrialized nations, between

5% and 20% of the population may be infected [1]. Influenza illness can range in severity from asymptomatic infection to mild respiratory illness to primary viral pneumonia and death [1–7]. More than 90% of influenza-related deaths occur in persons 65 years of age and older, but school-age children generally have the highest infection rates [2–7]. Although influenza virus infection may result in more severe illness than that caused by other respiratory viruses and have a greater impact on the population as a whole, individual cases of influenza cannot be diagnosed based on clinical information alone. Laboratory testing is required to differentiate influenza from other respiratory virus infections. Surveillance for influenza must take into account a constantly changing virus, the pervasiveness of infection, and the nonspecificity and range of clinical illness. Laboratory surveillance serves as the foundation of influenza surveillance and is necessary for the selection of appropriate vaccine strains. However, additional components that provide morbidity and mortality information are needed to provide a complete picture of the impact of influenza necessary to guide prevention, control, and mitigation policies. Descriptions of laboratory-based surveillance and systems to monitor outpatient illness, hospitalizations, and deaths due to influenza will be discussed. Specific examples from the United States (US) are used.

Components of influenza surveillance

Worldwide influenza surveillance is conducted through the World Health Organization (WHO)

Global Influenza Program that was conceived in 1947 and the WHO Global Influenza Surveillance Network that was established in 1952. The network currently consists of four international WHO Collaborating Centers for Reference and Research on Influenza and 116 laboratories in 87 countries recognized by WHO as National Influenza Centers (NIC). The NICs collect specimens from patients within their country with influenza-like-illness (ILI; defined as fever $>38^{\circ}\text{C}$ and either cough or sore throat [8]), either directly from physicians, clinics, and hospitals, or through a network of laboratories, for viral isolation. NICs perform preliminary analysis of influenza isolates, including virus typing and subtyping. Results are reported to WHO and made publicly available through a Web-based reporting system, called FluNet (<http://gamapservr.who.int/GlobalAtlas/home.asp>). A subset of the routine seasonal influenza isolates and all isolates for which the subtype cannot be determined are sent from the NICs to one or more of the four WHO Collaborating Centers for more detailed antigenic and genetic characterization and antiviral resistance testing. Seed viruses for vaccine production are obtained through this surveillance network.

The design of an influenza surveillance system should be based on the goals and objectives of surveillance. The goals of influenza surveillance at the international level may differ from those at the national, state, or local level. The primary goals of the international influenza surveillance network are to provide virologic data to inform twice-yearly trivalent vaccine strain selection and to rapidly detect and respond to human infections with novel influenza A subtypes that may have pandemic potential. Other goals of WHO's Global Influenza Program are detailed at <http://www.who.int/csr/disease/influenza/en/index.html>. National level goals may focus on measuring disease burden and impact to inform prevention and control policy development. Local jurisdictions may need information to inform patient treatment decisions and outbreak response. Additionally, whereas interpandemic influenza surveillance forms the foundation for pandemic surveillance, it is unlikely that those systems alone will be sufficient for detecting the initial introduction and spread of pandemic influenza or be able to fulfill all the information needs during a pandemic. Further

information on interpandemic surveillance as part of pandemic preparedness can be accessed at <http://www.who.int/csr/resources/publications/influenza/FluCheck6web.pdf>.

Regardless of the surveillance goals or objectives, a combination of virologic data and influenza-related morbidity and/or mortality components is typically needed. Several considerations should guide the selection of the clinical outcomes to be monitored and the sources of data to be used. Emphasis should be placed on collection of the minimum amount of data required in order to make public health decisions, collection of data that can be used by local, state, and national level public health officials, use of existing electronic data when available, and use of all the data that are collected. Sources of data frequently used for influenza surveillance include:

- Laboratory records
- Vital statistics records
- Emergency room or outpatient clinic visits
- Sentinel physician or clinic records
- Hospital admissions or discharge records
- School or workplace records
- Notifiable disease records
- Long-term care facility or other institution surveys and records
- Healthcare worker surveys

Laboratory surveillance

Laboratory surveillance is the foundation of influenza surveillance. In addition to providing basic information on the geographic distribution and temporal patterns of circulating viruses, the goals of influenza virologic surveillance include monitoring for antigenic changes in the viruses for vaccine strain selection, monitoring for antiviral resistance, and detecting novel influenza subtypes that pose a pandemic threat. Virologic data can be used in combination with morbidity or mortality data to provide estimates of the burden of influenza. Although influenza infection generally leads to more severe illness among adults than other respiratory viruses, individual cases of influenza infection cannot be distinguished with certainty from other respiratory virus infections based on clinical information alone. Laboratory testing is necessary to confirm the diagnosis but testing of all ill persons is neither feasible

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nor necessary. Methods available for the diagnosis of influenza include virus isolation (standard methods and rapid culture assays), molecular detection (reverse transcriptase polymerase chain reaction, RT-PCR, and real-time RT-PCR), detection of viral antigens (enzyme immunoassays, EIA, and direct or indirect immunofluorescent antibody [DFA or IFA] testing), commercially available rapid diagnostic kits, and less frequently, electron microscopy, and serologic testing.

Appropriate clinical specimens for influenza virus testing include nasal washes, nasopharyngeal aspirates, nasal and throat swabs, transtracheal aspirates, and bronchoalveolar lavage. For commercially available rapid diagnostic kits, the optimal specimen varies depending upon the kit used. Specimens may come from multiple sources: physician's offices, outpatient clinics, institutional outbreaks, emergency departments, and hospitals. Respiratory specimens collected and tested as a part of routine patient care rather than purely for surveillance purposes may contribute a large proportion of samples reported for influenza surveillance. Optimally, samples should be collected from both severely ill cases, such as those requiring hospitalization, and those with milder illness requiring only outpatient care, as the predominant virus type or subtype may differ with disease severity. Systematic sampling of ill or hospitalized persons within a defined population can allow for calculation of rates of disease. Laboratory surveillance may be enhanced during pandemic alert phases by targeted sampling of persons who, based on the epidemiology of the virus of interest as it is known at the time, are at increased risk for infection with a virus with pandemic potential.

Commercially available, rapid diagnostic tests and laboratory methods such as RT-PCR, real-time RT-PCR, EIA, DFA, or IFA can provide results quickly and are useful for patient management. However, viral isolates are necessary for antigenic characterization and susceptibility testing to antiviral agents. These tests have little immediate impact on the treatment of an individual, but provide data necessary for the selection of influenza vaccine strains and recommendations for antiviral drug use.

Although it is a rare event, detection of human infections with a novel influenza A virus is one of the most important functions of the WHO Global Influenza Surveillance Network. Detection of a novel

virus may occur as a result of increased surveillance among persons, such as swine or poultry workers or cullers, exposed to influenza-infected animals. Human infections with influenza A (H7N7) in the Netherlands [9], influenza A (H7N2) in the US [10], and influenza A (H7N3) in Canada [11] were detected as a result of increased surveillance of occupationally exposed persons during recognized poultry outbreaks. Other cases, such as the initial case of influenza A (H5N1) infection of a child in Hong Kong in 1997 [12] and influenza A (H9N2) in two children in Hong Kong in 1999 [13] were recognized during the course of the routine virologic surveillance performed as part of the WHO Global Surveillance Network. These viruses were initially identified as influenza A viruses that could not be subtyped with the standard reagents for identification of human H1 or H3 subtypes and were sent to one or more of the WHO Collaborating Centers for further identification. Once a new subtype is identified, reagents for detection of that subtype can be produced and distributed, if necessary. Because of the increased biosafety requirements posed by influenza A (H5N1) viruses [14], diagnostic testing has focused on methods such as RT-PCR that can be performed under biosafety level 2 conditions and can provide results in a timely manner. Commercially available rapid diagnostic tests to diagnose influenza A appear to be less sensitive for influenza A (H5N1) viruses [15,16]; testing with more sensitive and specific methods should be performed on patients suspected to have influenza A (H5N1) infection.

The US influenza virologic surveillance system provides an example of an in-country network of laboratories. A group of approximately 140 US WHO collaborating laboratories and National Respiratory and Enteric Virus Surveillance System (NREVSS) (<http://www.cdc.gov/ncidod/dvrd/revb/nrevss/index.htm>) laboratories report to Centers for Disease Control and Prevention (CDC) the number of respiratory specimens tested for influenza and the number that were positive by influenza virus type or subtype. The US WHO collaborating laboratories report the data by age group. The US WHO collaborating laboratories consist of all state public health laboratories, some local public health laboratories, and some hospital or academic center laboratories. NREVSS laboratories that are not also

WHO laboratories are primarily hospital laboratories. CDC compiles and analyzes data from the US WHO collaborating laboratories and NREVSS laboratories on a national and regional level each week. The data are included in a weekly national influenza activity summary posted on the CDC Web site www.cdc.gov/flu, and are reported to WHO via FluNet.

The US WHO collaborating laboratories also submit a subset of viruses they have isolated to CDC for antigenic and genetic characterization and antiviral resistance testing. Each laboratory is asked to submit a few isolates from early in the season, a few from peak influenza activity, some late season isolates, summer isolates, and any unusual isolates. Unusual isolates may include those that do not react as expected in testing, isolates that may be the result of animal to human transmission, isolates from unusually severe cases, or any influenza A isolate that the laboratory is unable to subtype.

Enhanced surveillance for influenza A (H5N1) virus provides an example of how laboratory surveillance can be focused to increase the probability of detecting the introduction of a novel influenza virus subtype into human populations. Influenza A (H5N1) viruses were first detected in humans in 1997; and again in early 2003 in Hong Kong; in January 2004 H5N1 human infections were reported in Vietnam and Thailand. By November 2006, the virus had been detected in more than 250 humans in 10 countries in Asia and Africa and hundreds of millions of birds were infected in numerous countries including some in Europe. The majority of human cases were associated with direct contact with sick or dead birds or their excretions. Most patients were severely ill and more than 50% of the cases were fatal. This information was used in the US to focus surveillance on severely ill patients with a recent travel history to an H5N1-affected country and direct contact with either birds or suspected or confirmed human cases. State public health laboratories were provided with protocols and training for real-time RT-PCR testing methods that allow for rapid (within 4 hours) detection and subtyping of influenza viruses including influenza A (H5) virus. Recommendations for enhanced surveillance will remain in place until the epidemiology of the virus changes, requiring adjustment in the case definition, or the threat of H5N1 diminishes.

Virologic surveillance frequently leads to changes in the seasonal trivalent vaccine composition, but in January 2006 virologic surveillance also led to a change in recommendations for influenza antiviral use. There are two classes of antiviral drugs effective against influenza viruses, the adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors (oseltamivir and zanamivir). Resistance against adamantanes can emerge rapidly during treatment, but during 1995–2002 global surveillance showed less than 2% of influenza A isolates tested were resistant to this class of drugs. Resistance increased to 13.3% during 2003, driven primarily by increased resistance of viruses isolated in Asia [17]. In the US, 1.9% of influenza A viruses were resistant to the adamantanes during the 2003–2004 season, 11% were resistant during the 2004–2005 season [18], and 91% were resistant between October 2005 and January 14, 2006. In response, CDC issued an alert in January 2006 that recommended that adamantanes not be used for treatment or chemoprophylaxis of influenza A in the US until there are data that indicate that circulating influenza A strains are susceptible to these agents [19].

Morbidity surveillance

Disease surveillance for influenza presents many challenges. Most persons infected with influenza do not seek medical care and remain unidentified; cases of influenza usually are not confirmed by laboratory tests, and in most areas, reporting of influenza is not mandated. Therefore, influenza disease activity must be measured or monitored indirectly. Since the impact of influenza on morbidity and mortality can differ and may not follow a parallel course depending on the circulating viruses and the population under surveillance (e.g., mortality may be low in some years in which there still are substantial numbers of visits to clinicians), monitoring more than one clinical outcome is necessary to obtain an understanding of the impact of influenza during a given influenza season.

The selection of the clinical outcomes to be monitored and the data sources to be used should take into account the availability of existing data sources, the healthcare structure, the ease of collecting and reporting the data, the potential for sustainable reporting, and the potential for collecting data

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that are reasonably representative of the groups of interest.

Sentinel outpatient surveillance

In its most simple form, sentinel surveillance for ILI among outpatients can provide early evidence of increases in influenza virus circulation and information on where influenza activity is occurring, track the course of influenza activity during the season, and serve as a source of samples for virus isolation. In situations where the population under surveillance is known, population-based rates of ILI can be calculated. If, in addition, samples are collected in the sentinel sites in a systematic manner, the proportion of ILI due to influenza can be determined, rates of influenza infection requiring medical care can be calculated, and the burden of influenza in terms of outpatient visits can be estimated.

In Europe, the countries reporting to the European Influenza Surveillance System (EISS) have national sentinel surveillance systems for collecting and reporting information on ILI, acute respiratory infection (ARI), or both; most countries collect this information by age group. The case definitions used for ILI or ARI differ slightly from country to country. Many of the European countries have a centralized and government funded system of medical care, and therefore the population under surveillance can be more accurately defined than in countries like the US with a largely private-sector healthcare delivery system. For the countries where the population under surveillance is known, population-based rates can be calculated and reported. This allows for better assessment of the differences in impact between age groups and between influenza seasons.

In the US, outpatient ILI data are collected through the US Influenza Sentinel Provider Surveillance Network, a collaborative effort between CDC, state and local health departments, and healthcare providers. In this system, states are responsible for identifying an influenza surveillance coordinator, recruiting and retaining sentinel providers, maintaining data quality, and providing testing of specimens from sentinel providers. CDC is responsible for coordinating and managing the network, maintaining the reporting systems, serving as a data repository, and analyzing and disseminating the data.

The system has grown more than fivefold from approximately 500 providers enrolled in 29 states reporting 1.8 million patient visits during the 1997–1998 season to approximately 2400 providers enrolled in 50 states reporting 12 million patient visits during the 2005–2006 season. The purpose of the sentinel provider system is to monitor ILI activity in the general population as a surrogate for influenza. Therefore, states recruit sentinel providers who will, in aggregate, see a broad mix of patients that are representative of the state population particularly with regards to age and geographic distribution. Any primary care provider is eligible to participate, including practitioners in family practice, internal medicine, pediatrics, infectious disease, obstetrics and gynecology, and emergency medicine. Participation is open to private providers, emergency departments, urgent care centers, college/university student health centers, and health maintenance organizations. Sentinel providers report weekly summary data including the total number of patient visits for any reason and the number of patient visits for ILI (fever $\geq 100^{\circ}\text{F}$ and cough or sore throat in the absence of a known cause other than influenza) by age group (0–4 yr, 5–24 yr, 25–64 yr, >65 yr).

Sentinel providers are encouraged to submit throat or nasopharyngeal swab specimens from a subset of ILI cases for virologic testing at the participating state laboratory. Providers are asked to limit specimen collection to 2–3 swabs taken during each of the following times/types of cases: (1) ILI cases at the beginning of the season, peak of the season, toward the season's end, and during the summer; (2) unusual clinical cases or unusually severe cases, and (3) outbreak-related cases. The virus isolation data are entered into the virus surveillance system. Due to the time lag in obtaining results (approximately a week for viral culture), the information obtained from viral culture results usually will not be useful to the provider for confirming individual cases of influenza but does provide information about influenza virus circulation in the community.

Data reported by sentinel providers are used to calculate the percentage of all patient visits due to ILI. These data are analyzed weekly on the national and regional level and are reported in the weekly influenza surveillance report. Because the strength of ILI surveillance and the proportion

of the population covered by the participating providers can vary widely from state to state, the national and regional percentages of patient visits for ILI are weighted relative to the population of the contributing states. The national and regional percent of visits for ILI is compared to national or regional baselines, respectively, and values above the baseline usually correlate with increased influenza activity. The baseline is obtained by (1) calculating a 3-week moving average of the laboratory surveillance data (the percent of specimens testing positive for influenza) for each week during the influenza surveillance season, (2) calculating the average percent of visits for ILI during the weeks in which <10% of specimens tested positive for influenza, and (3) adding two standard deviations to this mean. Weeks during which the percent of visits for ILI rises above the baseline can be interpreted as weeks during which there were excess visits to healthcare providers most likely attributable to influenza.

The US sentinel provider system is a very labor-intensive system and in many states it does not provide enough data to adequately represent influenza activity at the state or local level. CDC and state health departments are exploring the utility of various electronic data sources as adjuncts to sentinel provider data. Such data sources might include emergency departments or other syndromic surveillance systems or large managed care organizations.

Hospital surveillance

Hospital-based surveillance for influenza can be useful in tracking levels of severe illness related to influenza. As discussed earlier, it is helpful to collect viruses from hospitalized patients because they may differ from outpatient case isolates in the proportion of viruses from one subtype. Other hospital data that can be collected include discharge diagnosis, admission diagnosis, chief complaint, admissions defined using both clinical and/or laboratory criteria, total number of admissions regardless of diagnoses, or bed census (including information about cancellation of elective procedures).

Collection of hospital discharge diagnoses is useful in documenting the impact of influenza but lacks timeliness and is therefore more appropriate for studies. As an alternative, some surveillance systems have monitored hospital admission diagnosis or

chief complaint data, which can be available sooner than discharge data. However, admission data may not be coded or available in computerized files. Additionally, admission data and discharge data are prone to coding biases and errors.

The Emerging Infections Program (EIP) and the New Vaccine Surveillance Network (NVSN) in the US are examples of population-based surveillance for laboratory-confirmed influenza-associated hospitalizations. These systems involve collaborations between CDC, state health departments, and universities. EIP began influenza surveillance during the 2003–2004 season and focused on pediatric populations until the 2005–2006 season, during which surveillance was expanded to include all age groups. This system seeks to capture information from 60 counties in 12 metropolitan areas on hospitalizations of individuals with a positive influenza test conducted as part of routine patient care [20]. The NVSN began surveillance for influenza among children aged <5 years in three counties in 2000. Respiratory swab specimens are obtained from a systematically established sample of children hospitalized with fever or acute respiratory illness and does not rely on physician ordering of influenza testing [21]. Regardless of the system, once a case is identified additional information is obtained via laboratory and medical record review and in some cases parental and provider interview.

Every other week pediatric surveillance data from each system are analyzed, preliminary hospitalization rates are calculated, and a graph of the current and previous seasons' data is presented in the weekly influenza surveillance report. Additional analyses on complete data are performed at the end of the season and provide valuable information about the type of individuals with severe outcomes associated with laboratory confirmed influenza. Data from these systems were recently used by the Advisory Committee on Immunization Practices, the advisory committee to CDC that makes recommendations on vaccine use, to expand vaccination recommendations for persons with a broader group of underlying medical conditions and to children aged <5 years.

Another example of hospitalization surveillance in the US is BioSense, a system newly developed by CDC that focuses on capturing information contained in electronic hospital records systems.

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The initial focus is on obtaining chief complaint and diagnosis information from a small number of hospitals with plans to increase the number of participating hospitals and data elements to include laboratory, radiology, pharmacy, bed census, and emergency department clinical data. More information about BioSense is available at <http://www.cdc.gov/biosense/>.

Influenza activity level assessment

The WHO, the European Influenza Surveillance Scheme (EISS), and US Influenza Surveillance System each include reports of estimated levels of overall influenza activity. In the WHO and EISS systems, estimated levels of activity are reported for countries or regions of a country and in the US system estimated levels of activity are reported for each state. Standard definitions are used within each of these systems but the definitions vary from system to system, and within a single system the surveillance methods used to make the activity level determination may vary from country to country and state to state. Although these assessments are not strictly standardized, they do provide a level of local interpretation of influenza activity and surveillance data that may be lacking otherwise.

Participating countries can report their influenza activity level each week through WHO's internet reporting system, FluNet (<http://rhone.b3e.jussieu.fr/flunet/www/>).

Activity level definitions in the WHO/FluNet system are:

- *No activity*—no influenza viral isolates or clinical signs of influenza activity
- *Sporadic*—an isolated case of ILI or laboratory/culture confirmed cases in a limited area
- *Local outbreak*—ILI activity above baseline values with laboratory confirmed cases in a limited area
- *Regional activity*—outbreaks of ILI or laboratory confirmed influenza in one or more regions with a population comprising less than 50% of the country's total population
- *Widespread activity*—outbreaks of ILI or laboratory confirmed influenza in one or more regions with a population comprising 50% or more of the country's population

The EISS system activity levels are similar to those used by WHO. However, EISS incorporates a sec-

ond variable to describe the intensity of influenza activity in addition to the geographic distribution of influenza viruses. The intensity of influenza activity is described as low, medium, high, or very high.

The system in the US for reporting statewide activity is the State and Territorial Epidemiologist's Report. The state or territorial epidemiologists (or their designee) from each state, New York City, Washington, DC, and Puerto Rico report the overall level of influenza activity in the state or territory each week. The activity level definitions that have been in place since the 2003–2004 season are summarized in Table 19.1.

Each week the states' reports are displayed in a color-coded map of the US. The weekly maps provide information on spread of influenza across the country at a glance. At the end of each season, the number of states reporting regional or widespread influenza activity in a given week are graphed and compared to previous seasons to estimate timing of peak influenza activity in the country. The state data are the most widely disseminated and quoted component of the national influenza system. The system has minimal resources and operational requirements since it draws on data already collected for other purposes. Modifications to activity level definitions adopted in 2003 appear to have strengthened the correlation with virologic and sentinel provider surveillance data.

Other sources of morbidity data

Other events that may reflect levels of influenza activity include school or workplace absenteeism, including healthcare worker absenteeism, sales of over-the-counter or prescription medicines used to treat influenza or the secondary complications of influenza, increases in ambulance calls, and institutional outbreaks. Each of these systems has strengths and weaknesses. In particular, outcomes such as absenteeism are highly nonspecific, and should be interpreted with caution. However, absenteeism can be useful on a local level to spur further investigation and to monitor the community burden of disease. Over-the-counter drug sales and to a lesser degree prescription drug sales are also nonspecific and the cause of increases may be difficult and time consuming to determine. Nonetheless, these outcomes can complement other surveillance methods if the data are readily available.

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Table 19.1 Influenza activity level definitions in the State and Territorial Epidemiologist's Report, United States.

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

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

[†]Laboratory-confirmed case: case confirmed by rapid diagnostic test, antigen detection, culture, or PCR.

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

[§]Region: population under surveillance in a defined geographical subdivision of a state.

Surveillance for influenza and ILI in institutions helps the facility identify influenza outbreaks early and limit spread of influenza to patients/residents and staff. Institutional outbreak surveillance is another marker of influenza activity in the community.

Mortality surveillance

Mortality surveillance provides a marker for severity of disease. This information can help policy makers, the healthcare community, and the general public understand the serious consequences of influenza and both justify implementation of preventive measures such as vaccination and determine high-risk groups likely to benefit most from these interventions. However, most influenza-

related deaths are not due directly to the primary viral infection but are from complications such as secondary bacterial pneumonia or worsening of chronic health conditions such as congestive heart failure or pulmonary disease. As a result, most persons for whom influenza initiated the chain of events leading to death will not be tested for influenza at the time of death or even at the time of hospitalization and will no longer be shedding virus by the time they are brought to medical attention.

Most measures of influenza-related mortality are estimates based on calculating the number of deaths occurring above, or in excess of, the number expected for that time of year if influenza viruses were not circulating. Data are typically collected from death certificates and the outcomes most frequently

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used are pneumonia and influenza deaths, respiratory and circulatory deaths, or all cause deaths [2]. Counting only pneumonia and influenza deaths produces a very conservative estimate of influenza-associated mortality that likely underestimates the true impact of influenza, while using increases in deaths due to all causes attributes any seasonal increase in the number of deaths to influenza and likely overestimates the impact of influenza. Using respiratory and circulatory deaths as proposed by Thompson *et al.* includes pneumonia and influenza deaths and deaths from other causes such as congestive heart failure known to increase during influenza season and produces estimates of the impact of influenza between those obtained using other outcomes [2]. Estimates can be calculated using a variety of mathematical models, one of the more straightforward being rate difference models [22]. In rate difference models, the numbers of deaths during periods of influenza virus circulation are compared to those seen during periods of low influenza virus circulation and the difference is said to be the influenza-associated excess mortality. Some investigators use the summer months as the comparison period and others use the weeks in the fall and spring where little or no influenza virus is detected but other respiratory viruses are expected to be circulating. This period is referred to as the “peri-season” period [23]. As expected, models using a summer baseline produce higher rates of influenza-associated mortality than those using the peri-season as a baseline for comparison.

In the US, three systems are used to monitor influenza-related mortality. The 122 Cities Mortality Reporting System provides a rapid assessment of influenza mortality. Each week throughout the year the vital statistics offices of 122 US cities report the total number of death certificates filed for that week and the number of deaths for which pneumonia or influenza was listed as an underlying or contributing cause of death on the certificate. The number of deaths reported through this system represents approximately 25% of all deaths in the US. A robust regression procedure is used to calculate a seasonal baseline. If the proportion of pneumonia and influenza deaths for a given week exceeds the baseline value for that week by a statistically significant amount, then influenza-related deaths are said to be above the epidemic threshold.

The US mortality data are also available from the National Vital Statistics System (NVSS) of the National Center for Health Statistics (NCHS) at CDC. Data from the NVSS differs from that received through the 122 Cities Mortality Reporting System in several important ways. First, the NVSS data set contains information for >99% of all deaths occurring in the US. There is a separate record in the NVSS data set for each death. In contrast, a record in the 122 Cities System contains a weekly summary of the number deaths from a city. Basic demographic data, the date of death, and the underlying and contributing causes of death are included in the NVSS data allowing for a more detailed analysis and more accurate assessment of the timing of P&I deaths. The cause of death is classified using International Classification of Diseases (ICD) coding. The largest drawback of these data is the lack of timeliness; the data for a given year are not available until approximately 2 years later.

During the 2003–2004 influenza season, following the reports of several deaths in children associated with influenza infection, CDC requested voluntary reporting of influenza associated deaths in children <18 years of age from state health departments. In 2004, laboratory confirmed, influenza-associated deaths in children was added to the US list of nationally notifiable diseases. This is the only mortality reporting system in the US that uses a laboratory confirmed outcome and can directly produce population-based rates. The data are collected via a Web-based case report form that feeds into the National Notifiable Disease Surveillance System. Basic demographic information is collected along with information on preexisting health conditions and complications, including secondary bacterial infections, vaccination status, and laboratory testing methods. The informally collected information from the 2003–2004 season showed that 67% of the children that died did not have medical conditions that placed them in one of the existing high-risk groups for whom influenza vaccination is recommended, but 20% had other chronic health conditions [24]. The most common of these were neuromuscular problems and developmental delays. This information led to the expansion of influenza vaccine recommendations by adding as a high-risk group adults and children who have any condition (e.g., cognitive dysfunction, spinal cord

injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration.

Conclusion

Influenza surveillance is a collection of surveillance components rather than a single system. Laboratory surveillance should form the foundation for any influenza surveillance system but selection of other components should be driven by the goals and objectives set for the system and the anticipated uses of the data. The challenges of influenza surveillance are numerous: the viruses are constantly changing and the vaccine requires annual updates, both the number of people affected and the severity of disease can vary substantially, the symptoms of influenza are nonspecific and testing is necessary to confirm diagnoses, electronic data sources for surveillance are often not available, and the possibility of the emergence of a novel influenza subtype and pandemic disease requires constant vigilance. However, data collected through surveillance can inform outbreak response and patient treatment decisions and rapidly lead to changes in vaccination and antiviral drug use policy. Demands for timely influenza surveillance data will likely increase as influenza vaccination programs expand and will certainly increase in the event of a pandemic. Systems should be designed with enough flexibility to meet changing needs and to be robust enough to be sustainable in both interpandemic and pandemic periods.

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