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Review

Seasonal and pandemic influenza surveillance considerations for constructing multicomponent systems

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Abstract Surveillance for influenza is essential for the selection of influenza vaccine components and detection of human infections with novel influenza A viruses that may signal the start of a pandemic. Virologic surveillance provides the foundation from which this information can be obtained. However, morbidity and mortality data are needed to better understand the burden of disease, which, in turn, can provide useful information for policy makers relevant to the allocation of resources for prevention and control efforts. Data on the impact of influenza can be used to identify groups at increased risk for severe influenza-related complications, develop prevention and control policies, and monitor the effect of these policies. Influenza surveillance systems frequently monitor outpatient illness, hospitalizations, and deaths, but selection of influenza surveillance components should be based on the surveillance goals and objectives of the jurisdiction.

Keywords Influenza, morbidity surveillance, mortality surveillance, novel influenza A viruses, virologic surveillance.

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Introduction

Influenza viruses present unique challenges for surveillance. Surveillance for influenza must take into account a constantly changing virus, the pervasiveness of infection and the non-specificity and range of clinical illness. Laboratory surveillance serves as the foundation of influenza surveillance and is necessary for the selection of appropriate vaccine strains and rapid detection of novel subtypes in humans. However, additional components that provide morbidity and mortality information are needed to provide a more complete picture of the impact of influenza necessary to guide prevention, control and mitigation policies.

Components of influenza surveillance

Worldwide influenza surveillance is conducted through the World Health Organization (WHO) Global Influenza Program, which was conceived in 1947, and the WHO Global Influenza Surveillance Network, which was established in 1952. The network currently consists of four international WHO Collaborating Centers for Reference and Research on Influenza and 122 laboratories in 94 countries recognized by WHO as National Influenza Centers (NICs). The NICs collect specimens from patients with influenza-like illness (ILI) within their country, either directly from physicians, clinics, and hospitals, or through a network of laboratories, for virus isolation; the NICs perform preliminary analysis of isolates including virus type and subtype. Results of this testing is reported to WHO and made publicly available through a web-based reporting system, FluNet (http://gamapserver.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 also obtained through this surveillance network.

The design of an influenza surveillance system, as with any other surveillance system, should be based on the goals and objectives of surveillance. However, the goals of influenza surveillance at the international level may differ from those at the national level and may also differ from those at a state or other 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. National-level goals may focus on measuring disease burden and impact to inform prevention and control policy development while local jurisdictions may need information to inform patient treatment decisions and outbreak response. In addition, while interpandemic influenza surveillance should form 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 will be able to fulfill all the information needs during a pandemic.

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 collecting the minimum amount of data required in order to make public-health decisions, collecting data that can be used by local-, state-, and national-level public-health officials, use of existing electronic data when available, and using 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 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 detection of 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 nor necessary for surveillance purposes. 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, direct or indirect immunofluorescent antibody testing), commercially available rapid diagnostic kits, and less frequently, electron microscopy, and serologic testing. Test methods vary in terms of the level of staff skill and training needed to perform the assay, the cost of test equipment and reagents, the amount of time needed to perform the test and obtain results, and the sensitivity and specificity of the assay. These factors should be taken into consideration in both the selection of test methods for use in surveillance and the interpretation of results. For example, some commercially available rapid diagnostic tests for influenza require no special test equipment, can be performed in a physician's office by office staff with little or no laboratory training, and provide results in less than an hour. The ease of use and speed of rapid tests make them useful for patient management, but these tests have lower sensitivity and specificity than viral culture and RT-PCR, cannot provide influenza A subtype results, and frequently require collection of a second specimen if additional tests, including virus isolation, are to be performed. These factors, along with the cost per test, make exclusive use of rapid tests less practical for surveillance purposes. Other test methods such as viral culture or RT-PCR are performed in a laboratory setting by trained personnel and require an initial investment in laboratory equipment and training, but may have lower reagent costs per test than rapid assays. Results from RT-PCR testing can be obtained in a day, while viral culture results can take several days to more than 1 week. Although these methods, particularly viral culture, may be less useful for individual patient management because of the timeliness of results, they both provide distinct advantages for surveillance and population-level disease control recommendations. Influenza A subtype information can be obtained from both viral culture and RT-PCR. A subset of the specimens testing positive by RT-PCR can be placed in culture to provide additional isolates for antigenic characterization for vaccine strain selection and assessment of vaccine match, antiviral resistance testing, and for potential use in vaccine seed strain development.

Appropriate clinical specimens for influenza virus testing include nasal washes, nasopharyngeal aspirates, nasal and throat swabs, tracheal aspirates, and bronchoalveolar lavage. However, the optimal specimen for rapid diagnostic tests varies among the different test kits and the product insert should be consulted. Specimens for surveillance 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

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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 the estimation of disease burden. 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.

Although it is a rare event, detection of human infections with novel influenza A viruses is one of the most important functions of the WHO Global Influenza Surveillance Network. The recognition of human infection with a novel influenza A virus may result from testing of persons potentially exposed to influenza-infected animals such as those occupationally exposed or exposed at a public venue where animals are exhibited. Human infections with influenza A (H7N7) in the Netherlands,[1] A (H7N2) in the USA,[2] and A (H7N3) in Canada[3] 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,[4] influenza A (H9N2) in two children in Hong Kong in 1999,[5] and recent human infections with swine influenza in the USA[6,7] were recognized in 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 the human H1 or H3 subtypes. As part of the WHO protocol, they were sent to one or more of the WHO Collaborating Centers for further identification. Once the new subtype is identified, reagents for the detection of that subtype can be produced and distributed if necessary. Commercially available rapid diagnostic tests may be able to detect novel influenza subtypes such as the influenza A (H5N1) viruses, but, to date, are able to identify them only as an influenza type A virus and cannot differentiate the novel virus from the commonly circulating human influenza A virus subtypes. The rapid tests also appear to be less sensitive for influenza A (H5N1) viruses,[8] therefore results should be interpreted with caution and repeated testing with more sensitive and specific methods should be performed on patients suspected to have influenza A (H5N1) infection. Because of the increased biosafety requirements posed by influenza A (H5N1) viruses,[9] diagnostic testing for H5N1 viruses 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 compared to culture that must be performed under BSL 3 plus conditions and can take days to provide results. Expanded use of RT-PCR for the identification of influenza A (H5N1) viruses has led to a general increase in the use of molecular methods for influenza surveillance. While this allows for rapid and sensitive detection and identification of seasonal influenza viruses and more rapid recognition of unsubtypable influenza A viruses, it is important to maintain virus isolation capabilities. Viral isolates continue to be necessary for some assays such as the antigenic characterization and serologic testing used for vaccine strain selection and the antiviral resistance testing needed for patient treatment recommendations. The design of a virologic surveillance system should take these public-health needs into account and provide for the collection of specimens appropriate for virus isolation as well as other testing methodologies.

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) laboratories report to the 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 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 national and regional levels each week. The data are included in a weekly national influenza activity summary posted on the CDC website http://www.cdc.gov/flu and are reported to WHO via FluNet.

The US WHO collaborating laboratories also submit a subset of the viruses they have isolated to CDC for antigenic and genetic characterization and antiviral resistance testing. Each laboratory is asked to submit isolates from early in the season, a sample of the isolates obtained throughout the period of increased influenza activity, late season and 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 Viet Nam and Thailand. By October 2008, the virus was detected in humans in 15 countries in Asia and Africa and among birds 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 60% of the cases were fatal. This information was used in the USA 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 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 rimatadine) and the neuraminidase inhibitors (oseltamivir and zanamivir). Resistance against adamantanes can emerge rapidly during treatment, but during 1995–2002, global surveillance showed <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.[10] In the USA, 1·9% of influenza A viruses were resistant to the adamantanes during the 2003–2004 season, but resistance increased to 11% during the 2004–2005 season.[11] The proportion of US isolates tested from 1 October 2005 to 14 January 2006 that were resistant to adamantanes jumped to 91%. This increase led CDC to recommend that neither amantadine nor rimantadine be used for the treatment or chemoprophylaxis of influenza A infections in the USA for the remainder of the 2005–2006 season[12] and the recommendation remains in place as of October 2008.

Morbidity surveillance

Disease surveillance for influenza presents many challenges. The majority of influenza-infected persons do not seek medical care and remain unidentified; most cases of influenza are not confirmed by laboratory tests, and in most locations, reporting of influenza cases is not mandated. Therefore, influenza disease activity must be measured or monitored indirectly. As 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.

Morbidity surveillance is used to detect and monitor patterns of illness related to influenza virus circulation and gives a measure of the health impact that influenza is having in the community. 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 that are reasonably representative of the groups of interest. Emphasis should be placed on collecting the minimum amount of data required in order to make public-health decisions and inform policy and on using all the data that are collected. Depending on the disease outcome, the public-health objectives, and a country's healthcare system, sources of data for influenza morbidity surveillance could include:

- notifiable disease records;
- hospital admissions, bed census, or discharge records;
- emergency room or outpatient clinic visits;
- sentinel physician or clinic records;
- school or workplace records;
- health surveys;
- healthcare worker monitoring;
- institutional surveys and records.

Examples of surveillance using some of these data sources are given below.

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.

Information on visits for ILI or acute respiratory infections (ARIs) can be obtained from several different 'sentinel' healthcare sites such as physician offices, outpatient or hospital-associated outpatient clinics, university student health clinics, or emergency departments. Persons reporting the data can be physicians, physician assistants, nurse practitioners, or other healthcare staff. The case definition for

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ILI used by WHO is fever >38°C (100·4°F) and either cough or sore throat.[13]

In Europe, the countries reporting to the European Influenza Surveillance Scheme (EISS) have national sentinel surveillance systems for collecting and reporting information on ILI, ARI, or both and 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 more centralized and government-funded system of medical care, and therefore the population under surveillance can be more accurately defined than in countries such as the USA 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 USA, 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. 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. Healthcare providers from any practice type that provides primary care are eligible to participate, including 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.

The outcome of interest is the number of clinical illness cases consistent with ILI. The US ILI case definition is fever ≥100°F (37·8°C) together with cough and/or sore throat in the absence of a known cause other than influenza. Sentinel providers report weekly summary data including the total number of patient visits for any reason and the number of patient visits for ILI by age group (0–4, 5–24, 25–64, ≥65 years). In addition, CDC recommends all states provide sentinel providers with the option of submitting throat or nasopharyngeal swab specimens from a subset of ILI cases for virologic testing at the state laboratory at no charge to the provider or patient. Providers are asked to limit specimen collection to 2–3 swabs taken during each of the following times/types of cases: (i) ILI cases at the beginning of the season, peak of the season, toward the season's end, and during the summer; (ii) unusual clinical cases or unusually severe cases, and (iii) 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 for all local providers 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 on the national and regional levels once a week and 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 analysis of these data allows tracking of the progression and intensity of the influenza season on a national, regional, and state levels. 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 (i) calculating a three week moving average of the laboratory surveillance data for each week during the influenza surveillance season; (ii) calculating the average percent of visits for ILI during the weeks in which <10% of specimens tested positive for influenza; and (iii) 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 data from this system provide valuable information to track the timing and intensity of the influenza season at national and regional levels but it is a very labor-intensive system and, in many states, does not provide enough data to adequately represent influenza activity at the state or local level. To address both issues, CDC and state health departments are exploring the utility of various electronic data sources as adjuncts to the sentinel provider data. Such data sources include emergency departments and/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. It is also helpful to collect viruses from hospitalized patients as they can differ from those collected from outpatients, for example, 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 than weekly surveillance. As an alternative, some surveillance systems have monitored hospital admission diagnosis or chief complaint data, which can be available sooner than discharge data. As admission data often may not be coded or available in computerized files, analysis may be time-consuming. Both admission data and discharge data are prone to coding biases and errors.

In some sites in the USA, hospitalizations associated with laboratory-confirmed influenza are monitored. This surveillance occurs through the Emerging Infections Program (EIP) and the New Vaccine Surveillance Network (NVSN). Both networks are examples of population-based surveillance for laboratory-confirmed influenza-associated hospitalizations and involve collaborations between CDC, state health departments, and universities. However, there are several differences between the two networks. EIP 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.[14] The NVSN performs surveillance for influenza among children aged <5 years in three counties. 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.[15] Not surprisingly, the prospective sample collection system used in NVSN results in an approximately 40% higher burden of disease detected.[16] 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. During the influenza season, preliminary hospitalization rates are calculated, and compared to data from previous seasons. Additional analyses on complete data are performed at the end of the season and provide valuable information about persons with severe outcomes associated with laboratory-confirmed influenza. Data from these systems were 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.

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 to classify geographic distribution of influenza activity as no activity, sporadic, local, regional, or widespread. EISS incorporates a second variable to describe the intensity of influenza activity in addition to the geographic distribution. The intensity of influenza activity is described as low, medium, high, or very high. The activity-level 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. While 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.

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 its own strengths and weaknesses. In particular, outcomes such as absenteeism are highly non-specific, 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. Other systems such as over-the-counter drug sales and to a lesser degree prescription drug sales are also non-specific 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. Surveillance for influenza and ILI in institutions helps the facility to identify influenza outbreaks early and limit spread of influenza to patients/residents and staff. Institutional outbreak surveillance can also be another marker of influenza activity in the community.

Mortality surveillance

Mortality surveillance provides a marker for the 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 the not due directly to the primary viral infection but 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

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of death or even at the time of hospitalization or 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 used are pneumonia and influenza deaths (P&I), respiratory and circulatory deaths, or all cause deaths.[17] Counting only P&I deaths produces a very conservative estimate of influenza-associated mortality that likely underestimates the true impact of influenza, whereas 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.*[17] includes P&I 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 the other outcomes. Estimates can be calculated using a variety of mathematical models, one of the more straight forward being rate difference models.[18] 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, while 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.[19] 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 USA, 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 1/4 of all deaths in the USA. A robust regression procedure is used to calculate a seasonal baseline. If the proportion of P&I 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 at CDC. Data from the NVSS differ 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 USA. 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 of 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 USA that uses a laboratory-confirmed outcome and can directly produce estimates of population-based rates. Basic demographic information is collected along with information on pre-existing health conditions, 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 which influenza vaccination is recommended, but 20% had other chronic health conditions.[20] 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's 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 non-specific 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. Because of the concern raised by human infections with avian influenza viruses, particularly A (H5N1) viruses, worldwide influenza surveillance has improved in recent years. The increased laboratory containment levels required to safely culture influenza A (H5N1) viruses has led to a tremendous increase in the number of laboratories with the equipment and trained personnel to perform RT-PCR assays for influenza. This presents the opportunity for enhancement of not only the detection of H5N1 viruses but also surveillance for seasonal influenza viruses in countries where this was not previously possible. However, in many developing countries where the close and frequent contact between people and animals makes detection of novel influenza viruses in humans more likely, competing healthcare priorities and the lack of country-specific information and a full appreciation of the impact of seasonal influenza may make sustaining influenza surveillance difficult. Ebbing concerns about the emergence of H5N1 as a pandemic virus in developed countries and a corresponding reduction in support to high risk but resource-poorer nations could also pose a threat to recent surveillance improvements. However, even with the numerous challenges, 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.

References

1 Koopmans M, Wilbrink B, Conyn M *et al.* Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in commercial poultry farms in the Netherlands [see comment]. Lancet 2004; 363:587–593.

2 CDC. Avian Influenza Infection in Humans. 2006. Available from: http://www.cdc.gov/flu/avian/gen-info/avian-flu-humans.htm (accessed 12 January 2006).

3 Tweed SA, Skowronski DM, David ST *et al.* Human illness from avian influenza H7N3, British Columbia. Emerg Infect Dis 2004; 10:2196–2199.

4 Centers for Disease Control and Prevention. Isolation of avian influenza A(H5N1) viruses from humans – Hong Kong, May–December 1997. MMWR – Morb Mortal Wkly Rep 1997;46:1204–1207.

5 Uyeki TM, Chong YH, Katz JM *et al.* Lack of evidence for human-to-human transmission of avian influenza A (H9N2) viruses in Hong Kong, China 1999. Emerg Infect Dis 2002; 8:154–159.

6 Centers for Disease Control and Prevention. Update: Influenza Activity – United States and Worldwide, May 20–September 15, 2007. MMWR – Morb Mortal Wkly Rep 2007; 56:1001–1004.

7 Centers for Disease Control and Prevention. Update: influenza activity – United States, September 30–December 1, 2007. MMWR – Morb Mortal Wkly Rep 2007; 56:1287–1291.

8 Fedorko DP, Nelson NA, McAuliffe JM, Subbarao K. Performance of rapid tests for detection of avian influenza A virus types H5N1 and H9N2. J Clin Microbiol 2006; 44:1596–1597.

9 CDC-NIH. Interim CDC-NIH Recommendation for Raising the Biosafety Level for Laboratory Work Involving Noncontemporary Human Influenza Viruses. Excerpted from the Draft Biosafety in Microbiological and Biomedical Laboratories, 5th edn. 2006. Available from: http://www.cdc.gov/flu/h2n2bsl3.htm (accessed 12 January 2006).

10 Bright RA, Medina MJ, Xu X *et al.* Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern [see comment]. Lancet 2005; 366:1175–1181.

11 Bright RA, Shay DK, Shu B, Cox NJ, Klimov AI. Adamantane resistance among influenza A viruses isolated early during the 2005–2006 influenza season in the United States [see comment]. JAMA 2006; 295:891–894.

12 Centers for Disease Control and Prevention. High levels of adamantane resistance among influenza A (H3N2) viruses and interim guidelines for use of antiviral agents – United States, 2005–06 influenza season. MMWR – Morb Mortal Wkly Rep 2006; 55:44–46.

13 WHO. WHO Recommended Surveillance Standards, 2nd edn. 2006. Available from: http://www.who.int/csr/resources/publications/surveillance/WHO_CDS_CSR_ISR_99_2_EN/en/ (accessed 12 January 2006).

14 Schrag SJ, Shay DK, Gershman K *et al.* Multistate surveillance for laboratory-confirmed, influenza-associated hospitalizations in children: 2003–2004. Pediatr Infect Dis J 2006; 25:395–400.

15 Poehling KA, Edwards KM, Weinberg GA *et al.* The underrecognized burden of influenza in young children [see comment]. N Engl J Med 2006; 355:31–40.

16 Grijalva CG, Craig AS, Dupont WD *et al.* Estimating influenza hospitalizations among children. Emerg Infect Dis 2006;12:103–109.

17 Thompson WW, Shay DK, Weintraub E *et al.* Mortality associated with influenza and respiratory syncytial virus in the United States [see comment]. JAMA 2003; 289:179–186.

18 Thompson WW, Comanor L, Shay DK. Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. J Infect Dis 2006; 194(Suppl. 2):S82–S91.

19 Izurieta HS, Thompson WW, Kramarz P *et al.* Influenza and the rates of hospitalization for respiratory disease among infants and young children [see comment]. N Engl J Med 2000; 342:232–239.

20 Bhat N, Wright JG, Broder KR *et al.* Influenza-associated deaths among children in the United States, 2003–2004 [see comment]. N Engl J Med 2005; 353:2559–2567.

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