

REQUIREMENTS INTENT

This section describes each of the essential elements for an effective national influenza virologic surveillance system and explains the rationale for applying these requirements at the state, local and national level.

Sampling

Sampling Requirements: Provide year-round access to clinical specimens from ILINet providers and/or other primary care providers and clinical laboratories.

1. Establish a system that ensures efficient collection and timely flow of high quality specimens from the patient management tier of influenza surveillance to the CDC tier throughout the year.
2. Establish a representative network of specimen submitters using ILINet providers and/or other clinical primary care sources. Also collect specimens from hospital/clinical laboratories to ensure that a subset of specimens represents hospitalized patients. Capture unsubtypable influenza positives from clinical and commercial laboratories performing PCR methods that subtype currently circulating viruses.
3. Utilize a statistical, systematic approach to collect an appropriate, adequate number of specimens for testing that will provide reliable data with acceptable confidence limits to meet surveillance objectives and recommended thresholds of detection, including timely detection of rare/novel influenza events. The sampling methodology should limit sampling bias where possible.
4. Utilize sampling approaches that ensure specimens submitted throughout the entire surveillance specimen submission and testing process are representative of:
 - Virus types and subtypes,
 - The entire year,
 - Geographic diversity of the population,
 - Age of ILI patients,
 - Disease severity,
 - Targeted populations when necessary for specific investigations.
5. Send representative clinical specimens and/or virus isolates to CDC or a CDC-designated laboratory for national surveillance purposes, including annual vaccine virus selection, based on annual CDC criteria and guidance.

Requirement Intent

The primary goals of influenza surveillance are to detect rare/novel influenza events, provide viruses for vaccine strain selection and gain a broad understanding of domestic influenza activity. An adequate number of specimens should be tested to provide reliable data to meet the surveillance objectives at the recommended thresholds of detection previously described. Specimen sampling should be designed to enhance detection of rare/novel influenza events, while at the same time collecting a representative sample of routine influenza cases for overall seasonal situational awareness. Where possible, measures to limit sampling bias should be utilized.

Influenza testing occurs in a variety of settings, including physician office laboratories and primary ambulatory care settings, hospital and commercial laboratories and local and state PHLs. Human respiratory tract specimens and influenza test results data from all these groups contribute to the domestic US influenza virus surveillance system. This complex virologic surveillance landscape can be organized into five major testing tiers based on where testing is performed, as shown in Figure 1 (and in Appendix A).

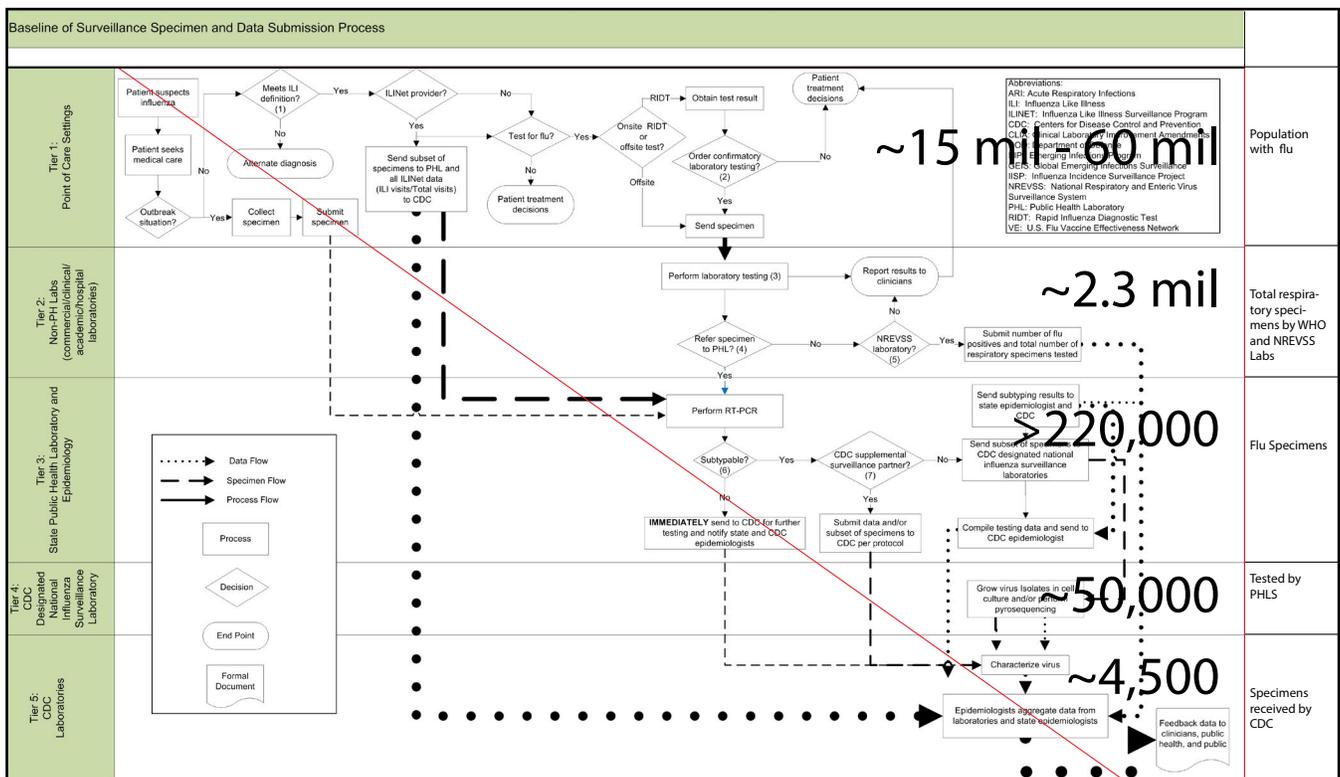


Figure 1: Surveillance Specimen and Data Submission Process. Full scale image available in Appendix A.

SAMPLING

The five tiers of influenza virus surveillance reflect the sequential flow of specimens and fundamental activities performed within each setting. At each level within the five-tier surveillance system, specimens are collected and tested by varying methods to diagnose influenza disease, monitor virus spread and characterize virus attributes. Since specimens are primarily obtained in the first tier, where they may or may not be tested, and then passed to subsequent tiers for diagnostic and/or surveillance testing, a sampling process takes place at each transfer point. As subsets of specimens flow from the patient management tier to the CDC tier, the number of specimens declines and testing becomes more advanced. The system also contains inherent biases due to the complexity of the funnel effect of the sampling system and the use of different test methods in the different tiers. The successive selection of specimen subsets for testing can impact the overall representativeness of samples that are ultimately used to conduct virologic surveillance and select vaccine candidates. The fact that each state surveillance system may impose distinct sampling criteria introduces unanticipated biases that are not always easily understood further complicating the aggregation of data. For instance, one state may request only screened rapid test positive specimens from surveillance partners, another state may request a combination of ILI unscreened and influenza screened positive specimens from surveillance partners impacting the percent positivity reported by the PHL each week.

Sample size and representativeness criteria should be established for sampling at each point in the system. Consistent compliance with sampling criteria will reduce the complexity of data analysis and interpretation at both state and national levels. Sources of bias should be considered and addressed if possible when selecting specimen providers, selecting test methods and analyzing and interpreting data.

a. Specimen providers and representativeness

Specimens for routine surveillance during influenza season should be obtained from:

- ILINet providers and other clinical primary care sources (Tier 1) who commit to regularly sending a subset of ILI patient specimens that have been systematically selected and are not screened positive (or if screened, a random mix irrespective of test results) to state or local PHLs for testing.
- Clinical laboratories (Tier 2) who submit specimens that have tested positive and negative by PCR based on jurisdictional sampling and sample size criteria. Additionally, a subset of culture positive specimens or virus isolates from clinical laboratories that perform virus isolation should be obtained.

Outside of influenza season, in addition to the routine samples submitted from a subset of ILI patients, participating specimen providers and clinical laboratories should send all specimens that test positive by RIDT or PCR to the PHL for confirmation and further characterization as well as specimens from patients with unusual respiratory illness, travel history or risk of exposure to animal origin viruses.

Feasibility and representativeness are the most important factors to consider when choosing specimen submitters. Criteria should be established for recruiting specimen providers and for submitting specimens that ensures specimens submitted throughout the entire testing

process (“funnel”) for virologic surveillance are representative of the population as a whole or of specific targeted populations as needed to meet surveillance objectives. More details on representativeness are provided in the Objectives: Thresholds and Representativeness section. The surveillance program should have the capability to establish targeted surveillance of specific populations if needed. Targeted surveillance (i.e., outbreaks, animal exposure, travelers outside the US) may be useful to answer specific questions, especially if a rare/novel influenza event or new virus is detected.

Every PHL (Tier 3) participating in virologic surveillance is responsible for submitting representative clinical specimens and/or virus isolates to CDC or CDC-designated laboratories for national surveillance purposes, including annual vaccine virus selection. Laboratories should submit specimens in a timely manner based on annual CDC criteria and guidance. Unsubtypable specimensⁱⁱⁱ require immediate action as they may reflect a novel virus with pandemic potential. These specimens are sent immediately to CDC for more comprehensive testing.

b. Sample Size

The number of specimens tested each week by state and local PHLs has typically been a function of the number of surveillance partners that participate in collection each week and the testing capacity of the PHL, in contrast to the number of specimens needed to meet the surveillance objectives at the recommended thresholds. In order to establish a more evidence-based approach, three statistical sample collection calculators have been created to estimate the desired number of specimens that should be tested to provide data with a defined confidence level for seasonal situational awareness, novel event and antiviral detection, and novel event investigation. These calculators can also be used to determine the confidence level of data derived from a particular sampling of ILI patient specimens, this option may be useful to estimate the level of confidence in the data obtained from the current (pre- right size) system, or when a jurisdiction is unable to achieve the desired sample size. The Sampling Implementation Guidance section and Appendix B provide more information on using the [sample size calculators](#).

““ The calculators are one of the best tools to come out of the right size process. They are complex but helpful to answer the question: “Are we testing enough?” ””

—Lisa McHugh, Influenza Surveillance Coordinator, New Jersey Department of Health

The sample size calculations are based on population size, desired level of confidence, margin of error and estimated or known prevalence or threshold for detection. More details on thresholds are provided in the Objectives: Thresholds and Representativeness section.

ⁱⁱⁱ Any influenza positive specimen that cannot be definitively typed and subtyped as a circulating seasonal influenza virus, influenza positive specimens producing non-standard or inconclusive results as defined in the CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel Instructions for Use package insert.

State and local PHLs are encouraged to use [sample size calculators](#) or pre-calculated sample size tables to achieve a more scientific, statistically based sample size that supports surveillance objectives. **Sampling approaches should be established to enhance detection of rare/novel influenza events based on national thresholds, while at the same time collecting a representative sample of routine influenza cases for overall situational awareness at the state level.** For many states, the number of samples to be tested for each of these objectives is very similar. For small population states, however, the number of samples necessary to achieve high confidence in situational awareness data at the state level will be much higher than the number of samples needed to contribute to national rare/novel influenza event detection thresholds.

Outside of influenza season, achieving statistical confidence may not be possible; therefore surveillance should shift to obtaining all specimens from participating clinical sites that have tested positive for influenza or from patients with unusual respiratory illness or travel history or risk of exposure to animal origin viruses, along with a subset MA-ILI specimens from routine surveillance providers.

c. Sample quality

Influenza surveillance programs and/or submitting laboratories should ensure proper collection, storage and transport of specimens. Proper specimen collection, handling and transport are critical to assuring the quality of results from any laboratory diagnostic test including diagnostic testing in support of virologic surveillance. Respiratory specimens should be of high quality and properly collected; specimen providers need to be trained in proper collection technique. Timely and efficient transport of specimens is often quite costly and must be adequately funded by the public health system for effective surveillance.

d. Bias

The influenza virologic surveillance system contains inherent biases due to the complexity of the sampling and submission selection processes (the funnel effect) of the sampling system and the use of different test methods in the different tiers. Sources of bias should be considered and addressed if possible when selecting specimen providers, selecting test methods and analyzing and interpreting data.

Laboratory Testing

Laboratory Testing Requirements: Detect, type, subtype, and characterize influenza viruses from clinical specimens in a timely manner using reliable laboratory methods.

1. Utilize molecular detection and subtyping methods (e.g., rRT-PCR) for influenza virologic surveillance.
2. Maintain instrumentation, personnel, expertise and adequate capacity to test the volume of specimens needed to achieve national, state and local surveillance objectives.
3. Ensure that staff members are knowledgeable in general principles of virology, molecular biology and surveillance, as well as appropriate specimen collection, handling, and transport methods.
4. Notify CDC immediately and ship unsubtypeable influenza A viruses to CDC within 24 hours of detection to rule-out novel viruses.
5. Routinely refer a representative subset of specimens (and viruses) to CDC or CDC- designated laboratory for genetic and antigenic characterization.
6. Maintain capability to rapidly adopt new molecular test methods or test modifications if a new influenza virus with pandemic potential emerges or when new technology provides improvements to virologic surveillance.
7. Maintain additional influenza testing capabilities (as defined in this document) as appropriate for the jurisdiction, or utilize shared services models to ensure access to testing.
8. CDC: Identify, characterize, and rapidly conduct risk assessments of emerging novel influenza viruses; develop, deploy and evaluate CDC assays to assure optimum performance; utilize sequencing methods; evaluate new technologies; and develop technical standards and guidance for virologic surveillance.

Requirement Intent

Influenza virologic surveillance, by definition, requires laboratories with the capability and capacity to detect, type, subtype and characterize circulating and emerging viruses. The introduction and widespread adoption of molecular methods has reduced the need to maintain classic virologic capabilities in every PHL. The essential components of laboratory testing described below takes into consideration the role of new technologies, the changing landscape of virology expertise in PHLs and the expected availability of national, state and local fiscal resources.

On the basis of a stakeholder assessment, the roadmap classifies virologic testing components into 1) **primary testing**: requirements that should be maintained and available at all PHLs involved in influenza surveillance, or 2) **additional testing**: additional surveillance testing capabilities that may be maintained based on jurisdictional needs and resources, or provided through a shared services model.

Primary Testing Method

PHLs performing virologic surveillance are expected to utilize molecular methods, such as rRT-PCR, as the primary method for influenza detection and subtyping. This is an ELC benchmark. Influenza rRT-PCR testing provides rapid, sensitive and accurate detection and identification of influenza viruses for routine influenza surveillance, outbreak detection and pandemic response. The CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel (CDC Flu rRT-PCR Dx Panel) is an FDA-cleared *in vitro* diagnostic assay that is manufactured and distributed by CDC to all qualified state and local PHLs engaged in influenza virologic surveillance testing. Although PHLs have the option to use commercial rRT-PCR assays, there are specific benefits to utilizing the CDC assay and CDC supplied reagents. This is a nationally recognized reference method and allows for standardization of influenza testing across all PHLs. The assay detects current influenza strains, is continually assessed and updated as needed to detect strain variations, and should detect novel viruses. The assay also allows for higher throughput testing algorithms to support outbreak and pandemic response. This method is consistent with the laboratory workforce's increasing proficiency in molecular testing methods. However, all PHLs engaged in influenza surveillance should also have staff knowledgeable in general principles of virology and surveillance, and appropriate specimen collection, handling, and transport methods.

Additional Testing Methods

There are additional testing methods that may be used to support influenza virologic surveillance. These include influenza virus culture, antiviral resistance testing of influenza viruses, influenza hemagglutination inhibition (HAI), immunofluorescence identification of influenza viruses and serology testing. Each of these methods has distinct purposes, advantages and disadvantages for both national and state surveillance. The determination to use any of these methods in PHLs should be made based on state and jurisdictional needs, detailed cost analysis, and identification of sustainable funding source (see Financial Resources Requirements Intent and Implementation Guidance sections).

Virus isolation has the advantage of producing quantities of virus sufficient for full antigenic characterization for determining vaccine match and conducting antiviral resistance testing.⁵ However, influenza virus culture is less sensitive and specific than rRT-PCR, and there are vast variations in the sensitivity of different cell culture lines, the growth characteristics of influenza virus strains and PHL practices and expertise. In addition, influenza virus culture is less rapid than influenza rRT-PCR and less adaptable to sudden surges in specimen numbers. Influenza virus culture must be maintained at CDC and a subset of PHLs.

Antiviral resistance testing is necessary to monitor the presence and level of antiviral resistance in circulating influenza viruses. These data inform patient management and treatment recommendations as well as national antiviral stockpile policies. Definitive antiviral resistance testing requires both phenotypic resistance testing, using a neuraminidase inhibition (NAI) assay (requires cultured viruses), and detection of genetic changes (drug resistance markers) by pyrosequencing and/or sequencing. Both of these test methods are available at CDC and a subset of PHLs. Performing pyrosequencing at a subset of PHLs provides a cost-effective and efficient approach to expanded surveillance screening. Supporting a limited number of testing sites allows for efficient updates to methods for viral mutations and training to develop the extensive expertise required to perform and interpret the test results and limits costs.

Influenza hemagglutination inhibition (HAI) testing remains a cornerstone of antigenic characterization for influenza vaccine strain selection. CDC maintains HAI expertise for antigenic characterization of

influenza virus culture isolates using specialized antisera. HAI tests using the WHO kit reagents that are provided to PHLs can be used to determine influenza type and influenza A subtype, but are not a reliable indicator of influenza strain or strain changes. Results of influenza HAI tests using WHO kit reagents may be over-interpreted as indicators of vaccine effectiveness and circulating strains. In addition, influenza HAI testing requires frequent practice to maintain expertise and proficiency in test performance and result interpretation.

Immunofluorescent antibody identification of influenza viruses is used in some PHLs for confirmation and identification of influenza viruses that have grown in cell cultures. Immunofluorescence (IF) testing is not as specific as rRT-PCR testing and requires a fluorescent microscope and staff with specialized expertise. However, influenza IF testing has the potential to identify novel strains of influenza grown in culture that evade detection by rRT-PCR.

Serologic testing is neither a routine surveillance nor diagnostic tool; it is currently used primarily by CDC or academic institutions for research purposes or retrospective seroprevalence studies. Testing requires staff with a high level of expertise and specialized reagents, there are currently no FDA cleared influenza serology tests.

Rapid influenza diagnostic tests (RIDTs) for the detection and identification of influenza viruses are used by many sentinel surveillance providers, other primary care sites, emergency departments as well as physician office and clinical laboratories. However, these tests are significantly less sensitive and specific than molecular assays.^{6,7} RIDTs may also be less reliable when new virus strains emerge. If PHLs choose to use RIDTs to serve diagnostic needs for selected patient populations, they should be aware of the limitations of these tests (e.g., the considerable variability of the positive and negative predictive values depending upon the prevalence of influenza in the community) and should follow guidelines provided by CDC (currently at www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm). If an important clinical decision will be affected by either a positive or negative rapid test result, the rapid test result should be confirmed by another test, such as rRT-PCR. Even if the PHL does not perform RIDTs, virology staff should maintain awareness of the performance characteristics of currently available RIDTs that may be used within their jurisdiction in order to provide seasonal guidance to clinicians, clinical laboratories and surveillance coordinators. PHLs or surveillance coordinators may also collect data from clinical sites using RIDTs to provide additional seasonal situational awareness data.

Direct specimen immunofluorescence using a direct fluorescent antibody method (DFA) involves testing clinical material taken directly from the patient and using fluorescent-labeled antibodies to detect influenza antigens that may be present. DFA can be performed quickly but is not as accurate as rRT-PCR testing and requires significant expertise and expensive fluorescent microscopes. In addition, results can be very subjective and are dependent on the individual reader's expertise.

Expanded testing for other respiratory viruses using molecular respiratory virus panels (RVPs) has become common in many clinical laboratories and is increasingly used in PHLs to provide jurisdictional and national information about circulating viruses that are associated with acute respiratory illness. While detection and identification of non-influenza respiratory viruses is not a component of national influenza virologic surveillance, data from these assays can aid in identifying the cause of non-influenza community illnesses or outbreaks. If surveillance for other respiratory viruses is performed to meet jurisdictional needs and resources are available, it is recommended that PHLs consider adopting molecular RVPs to replace less sensitive viral culture.

Data Management

Data Management Requirements: Report results to providers, epidemiologists and CDC.

1. Use electronic data systems that provide data in real time and utilize national standards (HL7, SNOMED, LOINC).
2. All data submitted should provide:
 - Specimen identifier and unique patient identifier,
 - The state where specimen was collected,
 - Date of birth of patient and/or age with unit (years, weeks, months, days),
 - Specimen collection date,
 - Specimen received date,
 - Test method performed,
 - Test result.
3. Laboratories that have established PHLIP capability should also provide the following data elements, if available:
 - Submitter Information,
 - Provider Identifier for the CDC Program (i.e., ILINet provider, EIP, other),
 - Current influenza vaccination status,
 - Antiviral treatment,
 - Travel information,
 - Patient death information,
 - Additional geographic information (e.g., county, city, zip),
 - Patient location at time of testing (inpatient, outpatient, long-term care facility),
 - Whether specimen was related to an outbreak,
 - Whether specimen was sent to CDC and if so, include specimen identifier,
 - Date of illness onset.
4. States should consider incorporating data from rapid test sites and/or clinical laboratories to supplement influenza surveillance state data.

Requirement Intent

Virologic surveillance in the US relies on a combination of data and specimens: data from laboratory tests performed at US WHO Collaborating Laboratories (WHO CLs) and National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories and specimens from patients with ILI that tested positive for influenza at PHLs are submitted to CDC for further characterization.⁹ There are approximately 85 US WHO CLs. The WHO CLs include 65 state and local PHLs supported by CDC, as well as several large tertiary care or academic medical centers.⁹ These laboratories have the capability to test for and report the type of influenza virus (A or B) and subtype of influenza A viruses (H1pdm2009, H3, and some novel subtypes), and provide both data and specimens/viruses to CDC.

The NREVSS system includes clinical, commercial, academic medical, and some PHLs. Most NREVSS laboratories that are not WHO CLs provide data on influenza laboratory test results by type and also subtype, when performed. According to the 2011 Right Size Virologic Surveillance Survey, those PHLs participating as a WHO CL submit non-influenza respiratory pathogen data into the NREVSS system.² The influenza data from the WHO collaborating laboratories and NREVSS play a large role in the weekly national reports generated by CDC in [FluView](#).

Additional influenza testing data from rapid influenza diagnostic testing sites and/or other clinical laboratories may be available to states and can help provide a fuller representation of influenza activity at the local level. These clinical sites have the capability to test for and report the type of influenza (A or B); some also utilize methods that can subtype influenza A (H1pdm2009, H3, H1).

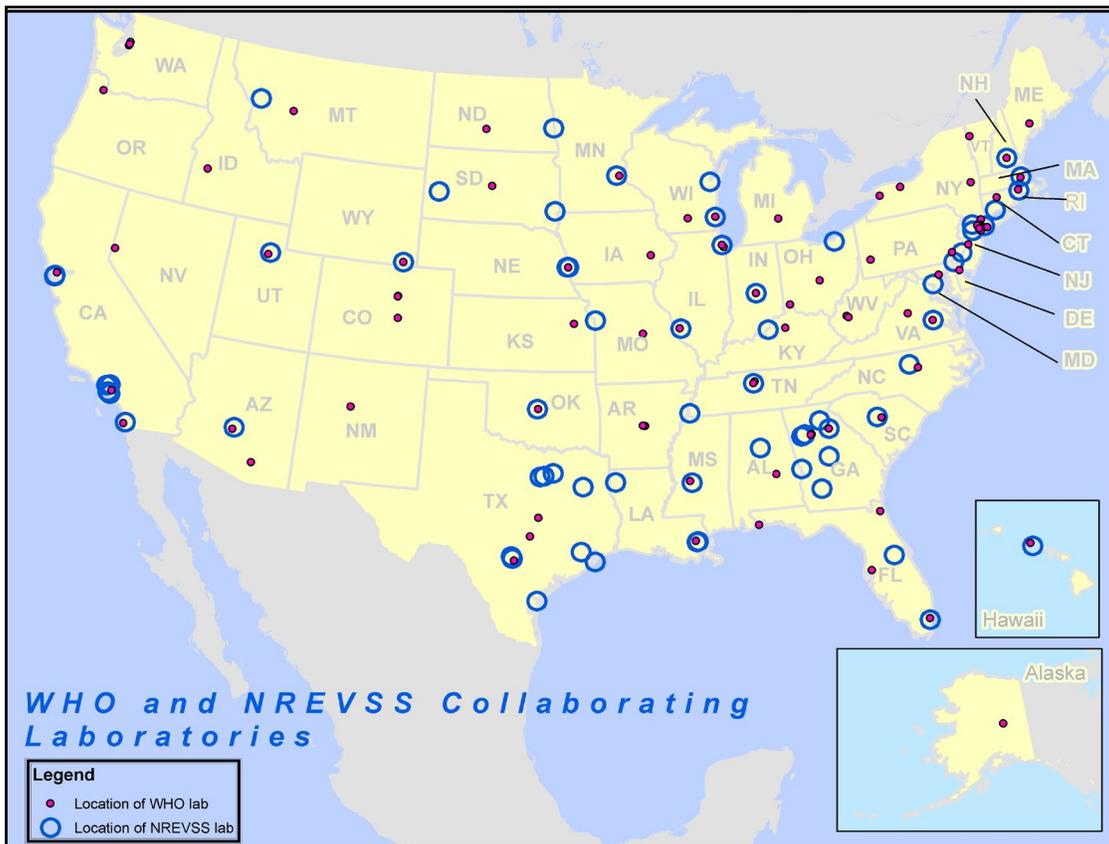


Figure 2. Representation of NREVSS Laboratories Across the US Source: CDC Unpublished Data.

Currently, influenza surveillance data is obtained both as aggregated data, using web entry methods, and as patient level data, using HL7 electronic laboratory reporting and comma delimited files. This dichotomy makes the data management, aggregation and linking of virologic and epidemiologic data challenging. However, this spectrum of reporting formats reflects a long history of virologic surveillance with varying technological solutions and capabilities of reporters.

The increasing availability of Laboratory Information Management Systems (LIMS) in PHLs makes it possible to establish automated electronic laboratory messaging of influenza test results to other public health entities (e.g., state epidemiology offices, other PHLs and CDC). The Public Health Laboratory Interoperability Project (PHLIP) provides PHLs with an electronic method to report laboratory test results to CDC using national standards such as HL7 Version 2.3.1 messaging, SNOMED vocabulary, and LOINC codes for laboratory tests. The PHLIP vision is to provide each state PHL (SPHL) with a viable option for electronic transmission of laboratory test data, in order to achieve interoperability between different systems and to exchange information in a useful and meaningful way. The PHLIP effort began in 2008, and the majority of state PHLs are now reporting influenza results electronically using PHLIP.

PHLIP is the preferred reporting mechanism to CDC for influenza and is considered a Right Size Influenza Virologic Surveillance requirement. It is understood that not all SPHLs have the same capabilities or resources to participate in PHLIP at present; however, PHLIP implementation should be the goal for all SPHLs and for county and local PHLs that participate in virologic surveillance. PHLIP offers many advantages, which include:

- Standardizes patient level reporting, improving data quality and simplifying data aggregation.
- Reports individual results in near “real-time.”
- Complies with other national electronic messaging solutions.
- Expands capability to report laboratory results for other pathogens using the same mechanisms for messaging.
- Reduces laboratory staff time required to collect and report laboratory results.
- Provides option for additional identifiers for type of specimen submitter (i.e., ILINet provider, EIP site, etc.) which is important to determine appropriate sample sizes.
- Supports use of shared services approaches among PHLs (i.e., PHLs specializing in influenza virus culture or antiviral resistance testing).

Electronic data messaging of specimen level data allows for more detailed analysis of the data and fuller understanding of potential biases in the data. Biases may include lack of population representativeness in the selection of patients for testing, screening of specimens before submission to PHLs and the quality of tests used for initial screening (refer to Sampling Requirements Intent and Implementation Guidance sections for more information).

Virologic Surveillance Data from Non-PHL Sources

The focus of virologic surveillance has been on data generated by the PHLs participating as WHO CLs in the US. However, influenza testing performed by clinical and commercial diagnostic laboratories may provide useful supplementary data, increasing the overall volume of testing and geographic representation. Existing virologic data from non-PHL sources, notably NREVSS, and some options for new sources of virologic data are discussed below.

NREVSS is managed by the CDC's Division of Viral Diseases. The system is the main source of national surveillance data for non-influenza respiratory viruses. Influenza laboratory testing data is also collected in NREVSS and shared with the Influenza Division for reporting as part of the national virologic surveillance report. Due to a rapid expansion of the reporting provider network in recent years, there were approximately 500 laboratories enrolled as NREVSS sites that reported influenza in the 2011-12 season. However, concerns about the sustainability of the expansion, along with a desire to maintain the historical number of reporters used in influenza virologic surveillance has resulted in use of only the data from 60 original participants. The reports submitted to NREVSS include laboratory-level information about the following: 1) number of specimens tested for influenza, 2) test method used (i.e., RIDT, culture, PCR) and 3) number of influenza positive specimens by influenza type and if available, by subtype.

Additional sources of influenza (NREVSS-like) clinical, hospital and/or commercial laboratory data can also be utilized and developed. For the same reasons that NREVSS data is useful at the national level, state laboratory networks can serve as a source of additional local level data for seasonal influenza situational awareness. Data from these sites may be transmitted electronically at the specimen level or in aggregate by a simpler method. Regardless of whether specimen level or aggregate data is received, necessary data elements would include:

- Date or week of specimen collection, receipt or test
- Total number of tests performed and influenza positives by:
 - Type,
 - Subtype (if available),
 - Age group.

Partnerships & Communication

Partnerships and Communication Requirement

Establish and maintain partnerships and networks enabling communications that support routine surveillance and emergency preparedness and response, data sharing and specimen sharing. Several interrelated partnerships are needed among the public health and healthcare communities for routine surveillance including

- CDC,
- State epidemiologist/surveillance coordinator,
- PHL,
- Clinical laboratories,
- Commercial laboratories,
- Clinicians,
- Rapid Influenza Diagnostic Testing (RIDT) sites.

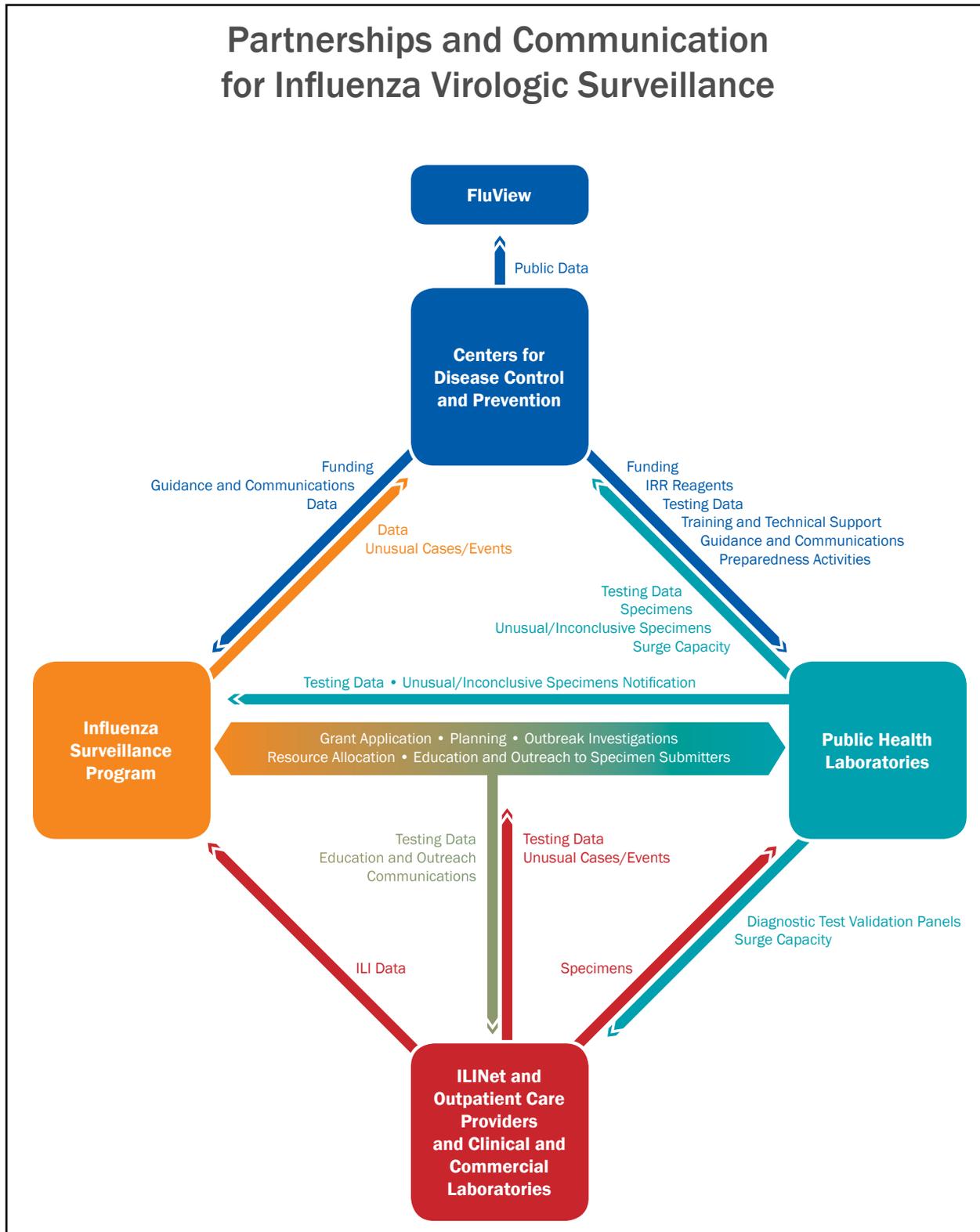
Requirement Intent

The US influenza surveillance system, which includes virologic, morbidity and mortality components relies heavily on partnerships across the local, state and national levels. As shown in Figure 3, these partnerships and networks are critical to communications that support routine surveillance, emergency response, data sharing and specimen sharing. The role and value of partnerships was very apparent in the highly effective public health response to the 2009 influenza A(H1N1) pandemic and has been documented in APHL's [Lessons from a Virus](#).¹⁰

The most important partnership for effective virologic surveillance is the relationship between **the PHL staff and epidemiology/influenza coordinators**. Data from the 2011 Right Size Influenza Virologic Surveillance Landscape survey to assess influenza-related activities at PHLs highlighted the value of this collaboration for jointly developing surveillance policy, strategies, and resource allocation.² This partnership also serves to improve communication, education and outreach to specimen submitters, data sharing and outbreak investigations. The roles and responsibilities of the laboratorians and epidemiology/influenza coordinators will vary across jurisdictions. Therefore, it is important that both parties have an understanding of each other's roles and agreement on the best approach to address each surveillance component.

Building and maintaining relationships with external partners has been identified as a pivotal contributor to the success of public health surveillance efforts. A strong **PHL/epidemiology/clinical-commercial-academic laboratory** partnership will support the formation of an effective specimen submitter network and enhance information sharing and outbreak response. Strong relationships among state epidemiology, PHL, and clinical partners are crucial to ensuring quality and consistent data and specimens for influenza virologic surveillance.

Partnerships and Communication for Influenza Virologic Surveillance



PARTNERSHIPS & COMMUNICATION

Figure 3. Essential Influenza Virologic Surveillance Partnerships and Communication. Effective virologic surveillance requires collaboration, communication, and coordination between various partners. Communication activities listed below are also facilitated by professional organizations such as APHL and CSTE.

Additional key PHL relationships are outlined in several documents, including APHL's [Core Functions of Public Health Laboratories](#), [Definition of a State Public Health Laboratory System](#), and CDC's [Public Health Preparedness Capabilities: National Standards for State and Local Planning](#).^{11,12,13} These relationships have also been included as elements in public health emergency response planning. Efforts to create state-based laboratory networks that interconnect to form a cohesive national system have been promoted in the context of [APHL's Lab System Improvement Program \(L-SIP\)](#), [Laboratory Efficiency Initiative \(LEI\)](#), [All-Hazards Public Health Emergency Preparedness \(PHEP\)](#) initiatives, the CDC/ Council of State and Territorial Epidemiologists (CSTE) [Competencies for Applied Epidemiologists in Governmental Public Health Agencies \(AECs\)](#) and the [Laboratory Response Network \(LRN\)](#) for more than a decade.^{14,15,16,17,18} The LRN structure for bioterrorism is represented by a pyramid, with clinical ("sentinel") laboratories as the foundation, PHLs as the primary members of the reference laboratory level, and CDC and other national laboratories at the peak of the structure (see Figure 4). The LRN pyramid demonstrates the interrelatedness of various partners in responding to potential bioterrorism threats and sets a foundation for partnerships and communication for other surveillance systems such as influenza virologic surveillance.

Partnerships between **CDC and PHLs** have also resulted in a number of important collaborative efforts including, but not limited to, informational teleconferences for PHLs, development of a "warm base" of diagnostics capabilities in PHLs for rapid deployment of tests (e.g., 2009 influenza A H1N1) and ongoing reagent and equipment support facilitated by the CDC, APHL and private industry, and others included in Figure 3. Similar relationships exist between **CDC and state based influenza surveillance coordinators**. Monthly conference calls and annual meetings allow for discussions about influenza circulation and potential areas of concern. Annual communications have been established between CDC, PHLs and epidemiology staff to ensure that all stakeholders are receiving relevant information at the beginning of each season, and working collaboratively toward common surveillance goals. Additionally, professional organizations such as APHL and CSTE provide programmatic and technical support to member states and facilitate communications among CDC, PHLs, and epidemiologists.

While partnerships between influenza surveillance programs and PHLs have been established to some degree in most states, maintaining these partnerships in the future may present a challenge as state resources dwindle and funding becomes more uncertain. Gaps in effective partnerships can result in significant but often poorly recognized negative impacts on virologic surveillance.

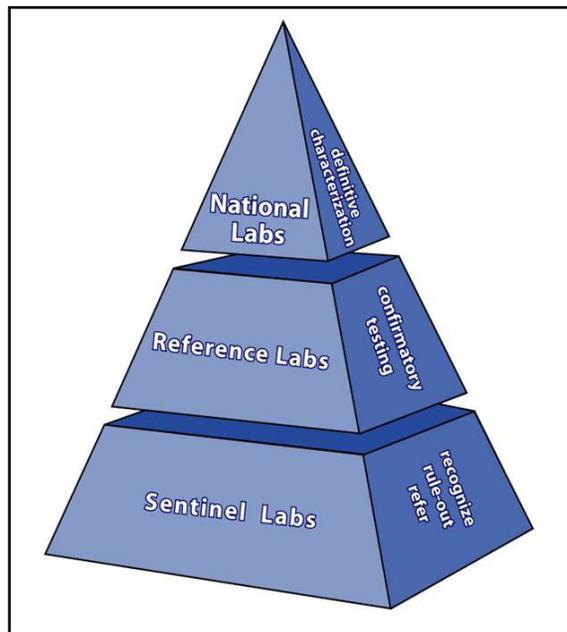


Figure 4. LRN pyramid showing the partnership relations between sentinel, reference, and national laboratories Laboratory Response Network (LRN)

Quality Management Systems

Quality Management Systems Requirement

Establish performance metrics, monitor performance and make improvements as needed to ensure national (and state/local) surveillance requirements are being met in an effective and efficient manner.

Requirement Intent

A quality management system can be defined as a coordinated activity to monitor and control organizational processes and resources. Both national and state/local virologic surveillance systems require monitoring and management of the various components that inform surveillance. Establishing and applying performance metrics encourages continuous improvement, demonstrates return on investments and helps to justify funding. It is important that CDC and state/local jurisdictions monitor activities related roadmap requirements as well as compliance with ELC and PHEP benchmarks.

State and local influenza programs and PHLs should monitor quality and consistency of specimen submissions throughout the system, data confidence in relation to sample sizes and representativeness and laboratory testing quality assurance parameters.

CDC should monitor reporting and specimen submissions to ensure national surveillance data are representative of influenza activity, meet current national needs across the entire country and that specimens are being submitted in a timely manner throughout the year to help inform annual vaccine virus selection. Additionally, monitoring resource allocation and usage in the context of surveillance test activities allows CDC to identify areas for improvement and justify funding for national and state/local surveillance systems. National quality monitoring efforts may include timeliness and consistency of testing data reported to CDC, influenza virologic surveillance specimen submissions to CDC and CDC-designated laboratories and utilization rates of CDC provided reagents.

CDC, PHLs and state/local surveillance programs should use data gathered through quality monitoring practices to identify and implement improvements and efficiencies as appropriate.

Surge Capacity for Influenza Surveillance, Novel Event Investigation and Outbreak Events

Surge Capacity Requirements

1. Maintain a year-round virologic surveillance system that is flexible and scalable for rapid, effective response to support diagnostic needs and case counts in rare/novel influenza event investigations, and enhance surveillance for outbreak and pandemic scenarios and has criteria to determine when to scale up and ramp down.
2. Incorporate the role and resource needs of the PHL in the state pandemic plan. PHL representatives should be part of state pandemic planning processes
3. Develop and maintain a laboratory pandemic surge plan that addresses criteria for specimen triage, algorithm changes to improve throughput, and resource needs (e.g. staff, equipment, space, reagents and supplies).

Requirements Intent

Virologic surveillance is vital to support rare/novel influenza event and outbreak investigations and pandemic response. Pre-event and during an event, communication and coordination between epidemiology and laboratory leadership is essential to develop, refine and change the strategy for virologic surge sampling and testing. However, the term “surge capacity” has many different meanings which can result in unrealistic expectations of the virologic surveillance system. While seasonal surveillance provides the warm base of expertise and infrastructure necessary to provide surge capacity, the response needed for a local outbreak investigation, emergence of a novel influenza virus or a pandemic response are qualitatively and quantitatively very different. The Institute of Medicine Medical Surge Capacity Workshop report grossly defines surge capacity as the ability to rapidly accommodate a large number of patients from a defined mass-casualty incident or pandemic, and considers surge capacity on a continuum with three distinct stages: conventional capacity, contingency capacity and crisis capacity.¹⁹ These medical surge definitions are adapted here to provide standardized terminology to improve planning and response:

- Conventional capacity: routine virologic surveillance capacity to test adequate sample size to produce meaningful data with reasonable confidence levels.
- Contingency capacity: minor adaptations are made that generally have limited impact on routine operations. This “spare” capacity must be maintained to deal with fluctuations in testing that may be necessary during a bad influenza season (e.g., increased hospitalizations, rapid transmission within the community, drifted virus), a local outbreak investigation or a rare/novel influenza event investigation. Efficient use of contingency capacity may require emphasis on targeted testing based on event specific criteria.

- Crisis capacity: a fundamental, systematic change into a system in which standards of operation are significantly altered. When crisis capacity is reached, the focus will shift to expanded hours of operation utilizing staff from other programs or areas of the laboratory, changes in testing algorithms and most importantly, significantly limiting testing based on event specific governance criteria.

These definitions of capacity relate to the equipment and supplies available and even more importantly to the staff needed to provide all the tasks required for specimen accessioning, processing, testing, data management and analysis. Therefore each jurisdiction may have different triggers that will cause a shift from one stage to another.

Novel Event/Outbreak Investigations

Following identification of a potential outbreak, a rare/novel influenza virus or other rare event, populations that will be targeted for testing will be determined based on:

- Epidemiologic criteria (e.g., exposure, geographic location, event specific risk factors),
- Clinical criteria (e.g., severe or fatal illness),
- Specimen sources (e.g., ILINet or other primary care providers, clinical laboratories using high performing assays).

Although epidemiologists will serve as gate-keepers for PHL testing, collaborative epidemiology-laboratory pre-event planning and event response is needed to ensure common understanding and expectation of contingency and crisis capacity. PHL influenza testing capacity models²⁰ and Right Size [Sample Size Calculators](#) can be used to identify system efficiencies and limitations. The APHL Infectious Disease Planning and Response Framework is another useful tool for planning.²¹

H1N1 Response: Lessons of the Virus

Public health labs opened their doors to let in specimens from clinical labs because they had the best test and were eager to fulfill their surveillance mission... You can't just hire a molecular biologist off the street. The layers of quality assurance involved in validation add critical steps to the process. Specific, sophisticated instruments and expensive reagents are required. Regulatory clearance can add time to the process. The subtleties don't always translate to the general public or political representatives. For them, the gold-standard is an immediate yes-no answer at the point of care.¹⁰

Pandemic Surge

In the event a novel virus emerges that is highly transmissible, the PHL will likely be the only resource for diagnostic testing at the start of the event, particularly if the commercially available tests do not reliably detect or differentiate the virus. As demonstrated in the 2009 H1N1 pandemic response, PHL testing capacity will be stretched by testing demands, rapidly reaching unsustainable crisis capacity. Effective governance for triage of cases eligible for testing at the PHL will be necessary. Epidemiologists, in collaboration with the PHL leadership, will need to manage the demand for diagnostic testing and ensure that surveillance testing that is representative of the relevant populations is prioritized so that effective response and control measures can be effectively implemented.

Even when diagnostic testing demand can be met by the clinical laboratory sector, the PHL will be the primary resource for virologic surveillance data. Therefore, the PHL should be represented in state pandemic planning activities. The role and resource needs of the PHL should be addressed in the state pandemic plan. Expectations for state and local epidemiologists to serve as gate-keepers for specimen testing demands should be coordinated in advance and defined in the plan.

All PHLs should develop and maintain an internal pandemic surge plan that addresses criteria for specimen triage, algorithm changes to improve testing and reporting throughput and resource needs (e.g., staff, equipment, space, safety, reagents and supplies).

Financial Resources

Financial Resources Requirements

1. State influenza surveillance programs and PHLs should have adequate funding to support virologic surveillance requirements.
2. State influenza surveillance programs and PHLs should coordinate planning and allocation of available funds (ELC, PHEP, EIP, state) to program and laboratory elements (staff, information technology, all supplies, reagents and equipment maintenance).
3. National, state and local programs and PHLs should have effective cost accounting practices to justify resource needs and efficiently allocate available funds.
4. CDC should have adequate funding to support CDC's national virologic surveillance activities as well as state/local surveillance activities that rely on federal funds.
5. Programs within CDC such as ELC and PHEP that provide funding to support other state and local programs should collaborate to ensure that changes in one program do not unintentionally impact other individual programs.

Requirement Intent

An optimal influenza surveillance system requires adequate resources to support all essential elements defined in this roadmap document. Sustaining the national, state and local components of this system is increasingly threatened by the decline in annual and pandemic response funding. Implementation of the right size virologic surveillance guidelines will help CDC, PHLs and surveillance programs maximize available resources, redirect resources as necessary and build new capacity as needed for optimal surveillance. Accurate assessments of the cost of virologic surveillance activities are critical to justify and prioritize funding.

Federal funding provided since 2005 to support pandemic planning, and supplemental funding made available during the 2009 H1N1 response have resulted in many improvements to the US influenza surveillance system. It is important to use available resources now to optimize systems for the future. Collaborative planning, grant proposal development and funding allocation between influenza surveillance programs and PHLs is essential to ensure all involved parties have an understanding of the costs associated with all aspects of influenza surveillance and that all virologic surveillance requirements are adequately resourced.

Surveillance is supported by several different funding streams, distributed at different times depending on source. Additionally, the cost of surveillance and the availability and allocation of funds for the different components of virologic surveillance varies across jurisdictions; these challenges can impact the overall effectiveness of the surveillance system. While funding is often cited as a key limiting factor, the true costs of virologic surveillance are not well defined, likely because of the complexity of the system. Optimizing resources and justifying funding requests will require better cost accounting at the national, state and local level.

Federal Funding Sources

- **ELC Cooperative Agreement:** Currently, state/local influenza virologic surveillance systems rely heavily on CDC funding resources. In particular, the ELC cooperative agreement program has been the primary funding source for surveillance at the state level, especially for supporting programmatic and laboratory personnel. All 50 states and several large cities receive funding from CDC to support US influenza surveillance goals via the ELC cooperative agreement program. The primary goals of the influenza component of the ELC program include: establishing and supporting ILI sentinel provider networks, providing timely ILINet data to CDC and maintaining laboratory testing and reporting capability and capacity for year round virologic surveillance. CDC supports public health influenza virologic surveillance through the ELC because the work of the PHLs contributes to national and global disease prevention efforts. Specimens submitted to CDC and CDC-designated laboratories contribute the viruses used to assess antigenic changes that impact vaccine effectiveness; these viruses are also frequently selected as seed strains for the manufacture of seasonal vaccines.

Sustainable Funding is Critical

At least once a year, the influenza virus changes slightly. It stays ahead of testing and research—and ahead of funding for testing and research. The changing virus is one side of the equation. On the other side is the changing levels of funding. Labs experience “roller-coaster” funding levels—a surge of money in response to a crisis and cuts when a crisis is behind.

“People think of a lab as a building—you build it and you walk away. But you need people who are trained, you need new equipment, you need to stay up-to-date with disease pathogens.”

Excerpted from Lessons from a Virus.¹⁰

While routine annual influenza surveillance principally relies on ELC and state funding, these federal funding programs also contribute to national virologic surveillance goals:

- **EIP:** Active population-based surveillance in ten states for laboratory confirmed influenza-related hospitalizations. EIP sites also conduct influenza vaccine effectiveness evaluations among groups for which the Advisory Committee on Immunization Practices (ACIP) recommends annual vaccination.
- **PHEP Cooperative Agreements:** Provides some funding for certain pandemic planning and response activities, including partner and clinical laboratory outreach, the purchase of laboratory equipment and supplies or support for specimen courier/transport systems.
- **Other special projects:** As resources permit, CDC supports additional studies and special projects such as the Influenza Incidence Surveillance Program (IISP). These programs help increase capacity for participants and provide valuable data for national surveillance.

Additional Federal Resources

In addition to funding, other resources are provided to states by CDC to help minimize the financial and resource burden on each jurisdiction. Listed below are some of the key non-financial resources that help CDC and state/local jurisdictions meet the surveillance requirements outlined in this roadmap document.

- **Influenza Reagent Resource (IRR):** Since 2009 CDC's IRR provides rRT-PCR reagents to qualified PHLs to help sustain rapid virus detection and subtyping capacity. This is a critical resource that significantly reduces the financial burden for state/local jurisdictions and ensures the timely availability of molecular testing reagents intended for virologic surveillance. The IRR is able to bulk purchase which may be more cost effective than individual state purchases. Financial support for ancillary reagents through the IRR is assessed on an annual basis and is based on the availability of funds. The direct material cost to CDC for each IVD CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel, including Influenza A/B typing and subtyping reagents, enzymes, extraction kits and plastics, is approximately \$14,000 (i.e., \$20 for each specimen tested).
- **CDC-Designated National Surveillance Laboratories:** CDC, in collaboration with APHL, has established enhanced capacity in several PHLs to provide antiviral susceptibility testing and influenza virus isolation that serves all PHLs. The virus culture capability supports expanded availability of viruses for antigenic and sequence-based characterization at CDC, providing data and viruses for annual vaccine virus selection.
- **PHLIP and Information Technology Support:** Technical assistance teams provide training, on-site assistance and follow-up consultation to assist PHLs implement PHLIP. Resources to assist PHLs implement PHLIP have come through CDC Pandemic Influenza funds provided to APHL, although recently additional support to implement similar standardized messaging initiatives have been made available through the CDC LRN, LEI, and Vaccine Preventable Disease (VPD) initiatives. The broad applicability of PHLIP to other programs and to other efforts to support "shared services" models among PHLs provides a path to sustainability for PHLIP; however, this will require ongoing focus and effort to ensure sustainable funding and technical support.
- **Technical Support and Training:** CDC subject matter experts are readily available to PHL and program staff to address clinical, operational and technical questions. Additionally CDC provides diagnostic testing of unsubtypeable and other specimens of clinical interest such as when antiviral resistance is suspected. CDC, in collaboration with APHL, has provided a variety of in-person technical training courses (i.e., PCR, pyrosequencing) for state and local jurisdictions at little or no cost to states to ensure the necessary expertise is readily available at PHLs.

It is critical that CDC be adequately funded to continue supporting state and national activities which ensure an effective national surveillance system. In return, states should ensure that they are meeting ELC, PHEP and other federal grant benchmarks to be good stewards of these resources.

As funding is always a limiting factor, every state will need to determine how to achieve influenza surveillance goals to meet national and state needs. Federal resources (funding, reagents) distributed to states need to be directed to activities that support overall national priorities. State/local capabilities beyond those recommended as essential to meet national virologic surveillance goals will require financial support from the state.

State Funding Sources

In addition to federal funding sources, many states also receive financial support from their state and/or local jurisdiction. These additional funds can be a critical funding stream for supporting state surveillance activities. The actual mechanisms and level of support varies across states. As data indicated in the [2011 Right Size Influenza Virologic Surveillance Landscape Survey](#), the amount of state funds expended in support of influenza surveillance varies greatly across states.² As previously described, it will become increasingly important for state funds to supplement federal funds for testing not deemed essential to meet national virologic surveillance goals. It is important that each state determine which virologic surveillance testing services are essential for their jurisdiction's needs.