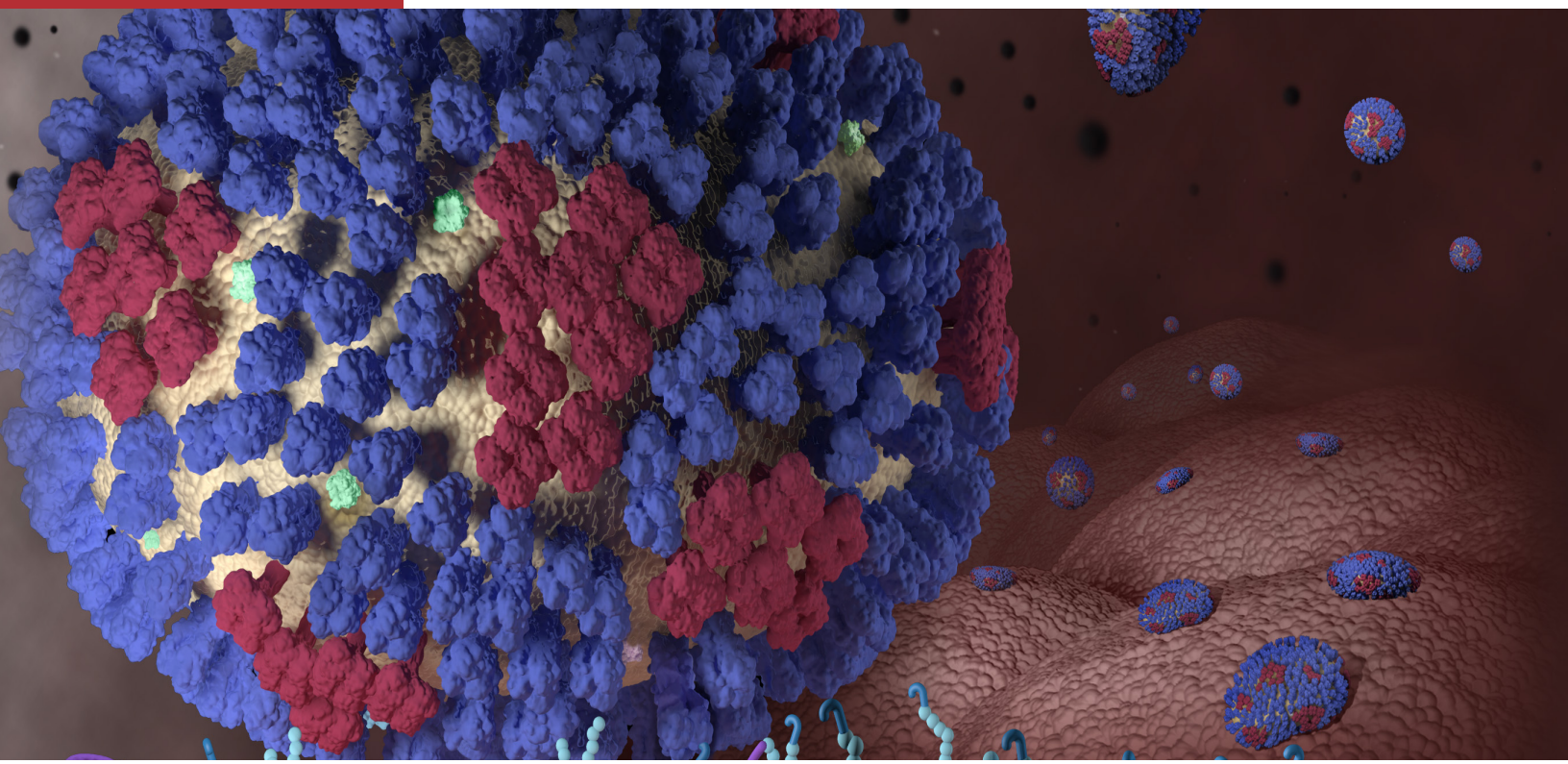
Influenza Virologic Surveillance
Right Size Roadmap

2nd Edition



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FORWARD

Comprehensive and timely information on influenza virus characteristics is critical for determining when the flu season starts and which viruses are circulating, for identifying and preparing viruses for use in influenza vaccines, and for detecting novel influenza viruses with potential for pandemic spread. In 2013, the first edition of the "Right Size Roadmap" was released. The document was the result of an initiative begun in 2010, led in partnership by the Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories (APHL) which engaged various stakeholders, including: epidemiologists, laboratorians, and influenza coordinators at local and state public health departments and at CDC; members and staff from the Council of State and Territorial Epidemiologists (CSTE); clinical and commercial laboratory associations; academic statisticians; and consultants in efficiency improvement. The goal of the effort was to support improved use of new tools for accurate and rapid molecular diagnosis of influenza, new opportunities for electronic communication of laboratory results, and to maintain or enhance virologic surveillance in the United States to detect first cases of emerging novel influenza A virus infection, such as infections with variant A(H3N2), or avian A(H5Nx) or A(H7N9) viruses. The resulting document provided a set of functional requirements to design and build an optimal virologic surveillance system, improve existing systems approaches, focus resources and efficiencies, inform policymakers, and justify state and local funding requests. It used statistical tools to determine the desired or acceptable level of surveillance and recommended efficiency approaches.

Today we have a standardized sampling strategy across public health and clinical laboratories that is nationally representative, ensures efficiency and data confidence, and includes characterizing both the antigenic and genomic properties of circulating influenza viruses. The landscape of influenza virologic surveillance has changed significantly since the first edition with national surveillance of influenza having transitioned to rely on public health laboratories submitting a set number of influenza positive samples weekly to one of the National Influenza Reference Centers (NIRCs), established in 2009, where additional characterization including virus isolation and whole genomic sequencing are done. Resultant isolates and data are then compiled by the CDC for further characterization and analysis. In addition to identifying the optimum "sampling" strategy, major improvements in sharing these data have taken place. In March 2009, five laboratories were routinely sharing specimen level data electronically with CDC. Today, all public health laboratories at the state level and some local public health and clinical laboratories send specimen level data electronically to CDC's Influenza Division. This increase has improved the timeliness and completeness of reporting for both seasonal influenza surveillance activities and the identification of novel influenza A viruses.

Influenza viruses are constantly changing, and efforts to monitor and characterize the virus similarly need to be flexible and adaptive to changes in healthcare, laboratory technology, and financial and staff resources. Equally, this second release will also change, and as such, continued input and feedback are invited to improve these recommendations for achieving a right size for influenza virologic surveillance. Future iterations will explore the possibility of utilizing the Right Size approach for non-influenza virus responses.

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The following work group led the development of the 2nd Edition, I*nfluenza Virologic Surveillance Right Size Roadmap*, the partner meetings and other project deliverables and provided subject matter expertise:

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INTRODUCTION

How much influenza surveillance do we really need? Do we need more or less laboratory testing? How do we know the surveillance data we have provide an accurate picture of what is really happening? These questions guided the Association of Public Health Laboratories (APHL), the Influenza Division of the Centers for Disease Control and Prevention (CDC), and state, local, and territorial health departments in an effort starting in 2011 to fine-tune the United States' influenza virologic surveillance and define the rationale, vital capabilities and optimal sample sizes ("Right Size" or "Right Sizing"). The desire for this project grew from the experiences during the 2009 H1N1 pandemic which demonstrated the need for a more strategic and evidence-based approach to virologic surveillance.

History of Right Size

Efforts over the years following the 2009 H1N1 pandemic resulted in the United States' Influenza Virologic Surveillance Right Size Roadmap (1st Edition)[1] in 2013, which consolidated requirements for all components of virologic surveillance into one document and provided tools to assess and improve the precision of the system in order to support disease surveillance, response and control efforts and policy decisions. The requirements described in detail in the 2013 Roadmap provided scientific, evidence-based justification for program and laboratory resources to support influenza virologic surveillance policy decisions. Implementation of the Right Size virologic surveillance guidelines assisted CDC and public health laboratories across the country to maximize available resources, redirect and build new capacity as needed for optimal surveillance and design a system based around common understanding and common goals.

Right Sizing Other Surveillance Systems

Since the launch of the 1st Edition, there has been considerable interest in right sizing other surveillance systems whether it be internationally for influenza or domestically for other pathogens. While the broad principles and requirements set forth in this document may be applicable to other surveillance systems, it is important to caution again the use of the sample size goals and calculators for anything other than the United States influenza virologic surveillance system. There are underlying assumptions in those calculations specific to the US influenza surveillance system that are known not to apply outside of this specific system.

The most visible products of the Right Size effort were sample size calculators aimed at guiding public health professionals determine how many specimens to test in various scenarios encountered throughout the influenza season. These calculators used a statistically based, standardized method to determine sample size and allowed health departments for the first time to base their testing volume on data driven indicators rather than laboratory capacity or other, less standardized methods.

2nd Edition Changes and Highlights

Since 2013, health departments, public health laboratories, CDC and APHL have used the Right Size Roadmap and calculators. These tools have been valuable to the advancement of influenza virologic surveillance; however, as influenza viruses are constantly changing, so are the needs for virologic surveillance. Technology has advanced in both laboratory science and data transmission, and this means that information needs for laboratorians and epidemiologists have changed as well. With this second edition, we aim to identify shifts in the availability and use of different data sources through a careful reevaluation and redesign. Like the 1st Edition, this document was developed with input from public health laboratorians, epidemiologists, CDC, and APHL.

While the core principles of influenza virologic surveillance have not changed since 2013, this document provides updated information where necessary, narrows the target audience to public health laboratory and influenza program staff, and attempts to clarify and simplify our messages, particularly around sample size goals. While the original sample size calculators were critical to defining our needs, APHL and CDC recognized their daily utility was limited and overly complex for jurisdictional purposes. As such, this document clearly outlines sample size goals by state in Appendix A, eliminating the need for jurisdictional use of the calculators. However, we recognize that some institutions find the calculators helpful for their own purposes and as such we are providing updated calculators with a simplified user interface to accompany this second edition release.

We learned from the implementation of the 1st Edition which requirements mattered most and how to better communicate our intentions. While the spirit of the requirements is unchanged, they have been updated in many places throughout the document to better reflect our priorities and clarify our intent. Where possible, we also sought to provide concrete examples of how to implement the requirements and will continue to provide updated examples and additional resources on APHL's website[2] to support this document going forward.

Implementing Right Size

The success of the influenza virologic surveillance system in any jurisdiction requires a strong partnership and collaboration between epidemiology and the public health laboratory (PHL), as well as active support of leadership and policy makers. The infrastructure, capabilities and surveillance system of each jurisdiction differ, requiring each to independently evaluate its current surveillance system and determine how to incorporate the Right Size surveillance recommendations. The Roadmap is designed to help identify "where you are, where you want to get to, and how to get there" to achieve more effective and efficient virologic surveillance.

The primary audiences for this Roadmap are state and local epidemiologists, influenza surveillance coordinators, PHL directors and other senior infectious disease laboratory staff responsible for coordinating policy decisions and relations with state epidemiologists regarding influenza virologic surveillance. The list of requirements and the descriptions of these essential elements will also be useful to policymakers and leadership making resource and funding decisions. Implementation guidance in this document will assist each jurisdiction in identifying strengths and weaknesses in the existing virologic surveillance system, determining the optimal amount of surveillance required, and identifying priority implementation activities. The Roadmap will also be a useful tool to assist in crisis management, whether the crisis is the result of detection of a novel virus, a large outbreak or a crisis of resources due to fiscal constraints. This is not intended to be a manual, but rather a guide to assist states in achieving an effective and efficient influenza virologic surveillance system.

The most important partnership for effective virologic surveillance is the relationship between the PHL and the epidemiologists/ influenza surveillance coordinators. Collaboration to implement these guidelines will be more successful if there is broad understanding of each partner's role.

This document includes three major sections:

- **Executive Summary:**
  - **Influenza Virologic Surveillance Right Size Objectives:** Defines the key surveillance objectives
  - **Virologic Surveillance Requirements:** Lists the essential components needed for effective, efficient, and economical influenza virologic surveillance
- **Sampling Objectives and Data Sources:** Describes sampling objectives and considerations to ensure that specimens are broadly representative of the population as a whole and establishes national thresholds for detection for each surveillance objective
- **Virologic Surveillance Requirements and Implementation Guidance:** Describes the essential elements for an effective national influenza virologic surveillance system in more detail and explains the rationale for applying these requirements at the local, state and national level; this section also seeks to provide suggestions to assist states with operationalizing the requirements

BACKGROUND

A comprehensive system for influenza surveillance is important to confirm when and where influenza viruses are circulating each year. It is also critical to identify changes in the circulating viruses which may impact vaccine effectiveness, influenza treatment decisions, annual vaccine virus selection and may even signal the emergence of a new virus with pandemic potential.

In the United States, the influenza surveillance system is a collaborative effort between CDC and its many partners in state, local and territorial health departments, public health and clinical laboratories, vital statistics offices, healthcare providers, clinics, hospitals, and emergency departments. The goals for national influenza surveillance include:

- Detecting the onset, duration, and geographic spread of influenza activity
- Measuring and describing the severity of influenza during a season
- Determining the populations affected and identifying groups at increased risk
- Monitoring the prevalence of circulating virus types and subtypes/lineages
- Evaluate genetic and antigenic changes in circulating influenza viruses in order to inform annual influenza vaccine composition
- Identifying and monitoring novel viruses that may have pandemic potential
- Providing data to guide clinical or public health interventions and control measures
- Providing information to key partners including:
    - Clinical decision makers
    - Policy makers
    - Public health officials
    - Emergency response officials
    - Media
    - The public

Specifically, testing data from public health and clinical laboratories provide information, which allow state and local health departments and CDC to achieve the following objectives of virologic surveillance:

- Early detection of novel influenza viruses
- Antigenic and genetic characterization of influenza viruses
- Annual vaccine virus selection
- Antiviral resistance detection and monitoring
- Situational awareness of circulating seasonal influenza viruses

At a minimum, virologic surveillance in public health laboratories includes the ability to:

- Access a representative sample of clinical specimens from outpatient providers—such as ILINet providers—and clinical laboratories
- Detect, type and subtype/lineage genotype influenza viruses from clinical specimens in a timely manner using the CDC Flu rRT-PCR Dx Panel
- Report results to specimen submitters, epidemiologists and CDC using standard electronic data systems
- Rapidly refer unsubtypable* specimens to CDC to identify or rule out novel influenza viruses
- Routinely refer a subset of influenza positive specimens to CDC or a National Influenza Reference Center (NIRC) laboratory for genetic and antigenic characterization and antiviral resistance testing
- Maintain expertise, a minimum level of readiness or capacity, and surge capabilities necessary for a pandemic response

This document is a “road map” to achieving an effective virologic surveillance system; it describes the system requirements and provides options and tools, including sample size goals, for decision-making processes and system implementation.

* Any influenza positive specimen that cannot be definitively typed and subtyped as a circulating seasonal influenza A virus, influenza positive specimens producing non-standard or inconclusive results as defined in the CDC Flu rRT-PCR Dx Panel Instructions for Use package insert.

The Right Size Approach

- Standardizes virologic surveillance practices
- Aids in the development and definition of public health surveillance priorities
- Provides requirements, resources needed and statistical calculators to aid in planning and justifying budget and resource requests
- Increases understanding and support of political leaders and the public
- Allows epidemiologists and laboratorians to establish virologic sample sizes more systematically for different surveillance objectives and scenarios based on minimum thresholds of detection and acceptable confidence levels
- Establishes common language between the laboratorians and epidemiologists resulting in improved communication between the two groups and better understanding of each other's needs
- Provides information to assist decision makers in analyzing the impacts of budget cutbacks on national surveillance objectives (e.g., decreased confidence levels, reduced pandemic preparedness capacity, etc.)

EXECUTIVE SUMMARY

Influenza Virologic Surveillance Right Size Objectives

Routine virologic surveillance allows situational awareness and novel influenza virus and antiviral resistance detection. It also provides specimens and viruses to CDC for annual vaccine virus selection. In order to promote a more statistically sound, systematic approach to virologic surveillance, thresholds for four key surveillance objectives were established in the first edition Roadmap. The thresholds are used to right size the virologic system by determining the number of specimens that should be tested or the amount of data that should be collected from clinical or commercial laboratories to ensure adequate statistical confidence level in surveillance data as well as detection of novel viruses at a point where prevention and control efforts can be effective.

1. **Novel Influenza Virus Detection**
   Detect a novel influenza virus among influenza positive surveillance specimens tested across all jurisdictions at a low enough threshold for implementation of effective intervention and control measures. This objective relates to the initial detection of a novel influenza virus, which generally occurs as part of routine surveillance.
2. **Vaccine Virus Selection**
   Monitor antigenic and genetic changes in currently circulating influenza viruses to inform vaccine virus selection.
3. **Antiviral Resistance**
   Detect antiviral resistant virus(es) among influenza positive surveillance specimens tested across all jurisdictions at a low enough threshold for implementation of effective intervention and control measures.
4. **Situational Awareness for Seasonal Influenza**
   Determine the beginning and end of the influenza season and monitor the prevalence and spread of influenza viruses throughout the year.

Virologic Surveillance Requirements

The requirements listed here are the essential components needed for effective, efficient, and economical influenza virologic surveillance. These requirements should be interpreted as example practices and not as criteria for receipt of federal funds. Each health department will need to determine how best to achieve both national and jurisdictional Right Size goals, including considering options for shared services.

A requirement is an essential component of virologic surveillance that is needed to produce reliable results and to achieve jurisdiction and national surveillance goals. These requirements can be used to design and build an optimal virologic surveillance system, improve existing systems, focus resources and efficiencies, inform policymakers, and justify national, state, territorial and local funding needs.

Sampling Requirements

Influenza programs and public health laboratories should:

1. Have a network of healthcare providers and clinical labs to ensure timely flow of high-quality specimens throughout the year. These specimens should be representative of:
    - Virus types and subtypes/lineages
    - The entire year
    - Geographic diversity of the population
    - Age of patients
    - Disease severity (e.g., hospitalized vs. outpatient)
    - Targeted populations when necessary for specific investigations.
2. Meet minimum sampling requirements to meet national surveillance objectives (Refer to your state's recommended sample size in Appendix A)
3. Send representative clinical specimens to CDC or National Influenza Reference Center (NIRC) laboratory for national surveillance purposes based on annual CDC/APHL criteria and guidance
4. Identify and resolve unsubtypable influenza positive specimens from any laboratory in your jurisdiction that performs subtype testing

CDC, at the national level, should:

1. Actively monitor laboratory testing data feeds and specimen submissions and as needed, solicit specimens to meet minimum sampling requirements for national surveillance objectives
2. Ensure antigenic and genetic characterization is performed on a sufficient number of specimens to meet sampling requirements
3. Provide guidance and support, as needed, in determining appropriate sample sizes for outbreak and novel virus situations
4. Support and maintain NIRCs in collaboration with APHL to provide additional virus characterization and capacity for influenza testing

Laboratory Testing Requirements

Influenza programs and public health laboratories should:

1. Detect, type and subtype/lineage genotype influenza viruses from clinical specimens in a timely manner using reliable laboratory methods
2. Use molecular detection and subtyping methods (e.g., rRT-PCR) for influenza virologic surveillance
3. Maintain instrumentation, personnel, expertise, and adequate capacity to test the volume of specimens needed to achieve national and jurisdictional surveillance objectives
4. 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
5. Notify CDC immediately and ship unsubtypable influenza A viruses to CDC within 24 hours of detection to either confirm or rule-out novel viruses
6. Routinely refer a representative subset of specimens to CDC and NIRCs for genetic and antigenic characterization
7. Maintain capability to rapidly adopt new test methods or test modifications if a new influenza virus with pandemic potential emerges or when new technology provides improvements to virologic surveillance
8. Maintain additional influenza testing capabilities (as defined in this document) as appropriate for the jurisdiction, or use regional consortium agreements to ensure access to testing

CDC, at the national level, should:

1. Identify, characterize, and rapidly conduct risk assessments of seasonal and emerging novel influenza viruses
2. Develop, deploy, and evaluate CDC assays to assure optimum performance
3. Optimize sequencing methods; evaluate new technologies
4. Develop technical standards and guidance for virologic surveillance

Data Management Requirements

Influenza programs and public health laboratories should:

1. Report results to providers, epidemiologists, and CDC
2. Use electronic data systems that provide data to CDC in (near) real-time and use national standards (HL7, SNOMED and LOINC)
3. Maintain the ability to rapidly modify messages as needed in an emergency response (e.g., add a novel virus)
4. Include the following data elements in reports to CDC:

   Required:
   - Specimen identifier
   - Unique patient identifier
   - Jurisdiction where the specimen was collected
   - ID number if the submitter is part of a CDC Program (i.e., ILINet provider, FluSurv-NET, other)
   - Date of birth of the patient and/or age with unit (years, weeks, months, days)
   - Race/ethnicity
   - Specimen collection date
   - Specimen receipt date
   - Specimen type
   - Test method performed
   - Test result

   If Available:
   - Gender
   - Current influenza vaccination status
   - Non-influenza respiratory virus test results
   - Antiviral treatment
   - Patient status at time of testing (inpatient, outpatient, long-term care facility)
   - Travel information
   - Patient death information
   - Additional geographic information (e.g., county, city, zip code)
   - Whether specimen was related to an outbreak
   - Whether specimen was sent to CDC and if so, include specimen identifier
   - Date of illness onset
   - Pre-screened test result
   - Pregnancy status
5. Monitor and use clinical testing data to achieve situational awareness goals

CDC, at the national level, should:

1. Support and maintain infrastructure for standardized, electronic reporting of laboratory results and surveillance data
2. Provide updated mapping and encoding guidelines, as needed

Partnerships and Communication Requirement

Influenza programs, public health laboratories and CDC should establish and maintain partnerships and communication networks which support routine influenza surveillance, data sharing, and specimen sharing that can be used for emergency preparedness and response. These partnerships and communication networks are needed at various levels among and between public health and healthcare communities including:

- CDC
- Influenza surveillance coordinators
- State and territorial epidemiologists
- Public health laboratories

- Clinical laboratories
- Commercial laboratories
- Healthcare providers
- Infection preventionists

Quality Systems Requirement

Influenza programs, public health laboratories, and CDC should establish performance metrics, monitor performance on a routine basis and make improvements as needed to ensure national and jurisdictional surveillance requirements are being met in an effective and efficient manner.

Surge Capacity Requirements

Influenza programs, public health laboratories, and CDC should:

1. Maintain a year-round virologic surveillance system that is flexible and scalable for rapid, effective response to support diagnostic needs in novel influenza virus investigations, as well as enhanced surveillance for outbreak and pandemic scenarios. The system should also have criteria to determine when to scale up and ramp down the response
2. Ensure that PHL representatives are included in state and federal preparedness and pandemic planning activities. Address the role and resource needs of the PHL in state/jurisdictional pandemic plans
3. Identify key partners and preparedness activities, including validation of new testing methodologies, biosafety, regulatory requirements, training, information dissemination, specimen collection and transport guidance, and reporting message modification
4. Develop and maintain a laboratory pandemic surge plan that is integrated into a laboratory-wide continuity of operations plan (COOP)
5. Establish mechanisms to determine and implement a sampling strategy for investigation following detection of a novel influenza virus. Consider the potential scenarios that may define sampling approaches, such as the need to identify additional cases and detect person-to-person transmission. Consider targeted surveillance options including clinical severity criteria, exposure risk, number of hospitalized cases/deaths and other event specific needs
6. Establish criteria for specimen triage and decision points for performing diagnostic testing and/or expanding virologic surveillance testing. Draft scenario specific scale up and ramp down criteria that can be quickly applied when a novel influenza virus is detected or an outbreak occurs
7. Define laboratory testing algorithms and trigger points that may be implemented to accommodate the influx of surveillance and diagnostic specimens
8. Periodically assess laboratory contingency and crisis surge capacity
9. Identify and address expectations to support diagnostic testing needs, including potential support to assist clinical laboratories validate tests for a novel virus

Financial Resources Requirements

Influenza programs and public health laboratories should:

1. Coordinate planning and allocation of available funds to program and laboratory elements (staff, information technology, supplies and equipment maintenance)
2. Have effective cost accounting practices to justify resource needs and efficiently allocate available funds

CDC, at the national level, should:

3. Coordinate distribution of available federal funds to states across multiple programs (e.g., ELC and PHEP) to minimize unintentional gaps and ensure federal priorities are supported and sustainable

SAMPLING OBJECTIVES AND DATA SOURCES

Routine virologic surveillance allows for situational awareness and novel influenza virus and antiviral resistance detection. It also provides specimens and viruses to CDC for annual vaccine virus selection. Efficiency is achieved by using the same specimens to address multiple surveillance objectives when possible (e.g., the same surveillance specimens can be used to address both seasonal situational awareness and novel influenza virus detection objectives). However, the surveillance program should also have the capability to establish targeted surveillance of specific populations if needed.

In order to promote a more statistically sound, systematic approach to virologic surveillance, thresholds for four key surveillance objectives were established in the first edition Roadmap.* In this context, a threshold is defined as the level which triggers some action. The action may be as simple as defining a point in the influenza season or initiating an investigation following detection of a novel virus, such as those defined in the CDC's Pandemic Intervals Framework.[3] The thresholds are used to right size the virologic system by determining the number of specimens that should be tested or the amount of data that should be collected from clinical or commercial laboratories to ensure adequate statistical confidence level in surveillance data as well as detection of novel viruses at a point where prevention and control efforts can be effective. In some situations, systems might be sized to be more sensitive than the threshold, particularly if the same specimens are used to meet multiple goals; this is considered acceptable and provides additional assurances that the thresholds remain achievable.

Influenza Virologic Surveillance Right Size Objectives

Novel Influenza Virus Detection

Detect a novel influenza virus among influenza positive surveillance specimens tested across all jurisdictions at a low enough threshold for implementation of effective intervention and control measures. This objective relates to the initial detection of a novel influenza virus, which generally occurs as part of routine surveillance.

Vaccine Virus Selection

Monitor antigenic and genetic changes in currently circulating influenza viruses to inform vaccine virus selection.

A **threshold** is defined as the level which triggers some action.

Antiviral Resistance

Detect antiviral resistant virus(es) among influenza positive surveillance specimens tested across all jurisdictions at a low enough threshold for implementation of effective intervention and control measures.

Situational Awareness for Seasonal Influenza

Determine the beginning and end of the influenza season and monitor the prevalence and spread of influenza viruses throughout the year.

* The sample sizes for the start of season were set using the state with the largest population, California, and an assumption of 10% positivity and 2.2% ILI. For peak of season, goals were set using an assumption of 5% ILI and 30% positivity. The sample size goals are approximate goals so slight variations in these assumptions should not affect jurisdiction's sampling practices.

Right Size Thresholds to Achieve Influenza Virologic Surveillance Objectives

The national influenza surveillance thresholds are the levels at which our system needs to be sized to detect specific events so that appropriate action can be taken. They are documented here as the rationale for the sampling goals outlined in **Appendix A**.

Objective: Novel Influenza Virus Detection

National Threshold	High Season (Peak): 95% confidence for the detection of at least one novel virus among influenza virus positive specimens per week if the novel virus prevalence is 1/700 or 0.14% • Shoulders of season (acceleration/deceleration phase): 95% confidence for the detection of at least one novel virus among influenza virus positive specimens per week if the novel virus prevalence is 1/200 or 0.5% • Summer/off-season: 95% confidence for the detection of at least one novel virus among influenza virus positive specimens per week if the novel virus prevalence is 1/4 or 25%; the goal is to reach at least this level for all weeks throughout the year (52 weeks)
Specimen Considerations	Specimens used to achieve this objective must be tested in a PHL using the CDC Flu rRT-PCR Dx Panel. The performance characteristics of the CDC Flu rRT-PCR Dx Panel against currently circulating viruses are continuously monitored to produce a reliable result that would indicate a potentially novel influenza virus. • Appropriate specimens include both unscreened specimens and prescreened positive specimens. Specimens previously tested in a clinical laboratory that are positive for influenza can be referred to the PHL for testing allowing jurisdictions, particularly those with large populations, to meet this goal in a more efficient manner. • Generally speaking, you should set your specimen submission guidance to exceed your 1/700 goal. You need to consider a variety of factors such as the number of specimens needed to meet your goal, the number of participating specimen submitters, and past experience with submitters' compliance. • For example, if your goal is to test 50 positive specimens a week, and you have 7 participating submitters, you may want to request that they each submit up to 10 influenza positive samples per week. If all are able to submit the maximum in a given week you will exceed your goal, but if some sites have fewer than 10 to submit or are unable to submit, you may still reach your goal. The guidance can be adjusted annually based on past experience.
Rationale	The goal is to keep a relatively constant level of ability to detect a novel influenza virus throughout the year. When prevalence is high you have to test more to identify a single novel virus and when it is low less testing is required. • 1/200 approximates the level at which H1N1pdm2009 influenza virus was first detected in April 2009, a time at which seasonal influenza was declining. A historical analysis of multiple seasons was performed using an average seasonal curve and the 1/200 threshold as a benchmark. To maintain a similar level of detection when influenza virus circulation is high, 1/700 was determined to be an appropriate threshold for peak of season. • The goal of reaching the 1/700 threshold for a minimum of four weeks per season was determined by looking at the number of weeks in which jurisdictions met their 1/700 goal in previous years. In seasons with low levels of influenza virus circulation, the median numbers of weeks that jurisdictions achieved their specific goal was four. • When there is low circulation of influenza viruses (e.g., summer), 1/4 is the lowest prevalence we can detect with 95% confidence.

Objective: Vaccine Virus Selection

National Threshold	95% confidence for the detection of at least one antigenic drift variant virus within an influenza A subtype or B lineage when its prevalence is 3% among influenza positive specimens of that specific subtype/lineage over a one-month time period.
Specimen Considerations	This objective is achieved with influenza positive specimens submitted to CDC and NIRCs by PHLs re broadly representative of viruses circulating within a jurisdiction based on: • Timeliness – the most recently collected viruses. • Geography – representative of the entire jurisdiction. • Age – includes viruses from all affected age groups • Disease severity – representative of the range of medically attended disease severities from outpatients to fatal cases.
Rationale	CDC and APHL defined these thresholds to serve as the routine baseline. CDC will provide guidance on specimen submission requirements at the beginning of each season. Every PHL participating in virologic surveillance is expected to submit specimens to CDC or a NIRC in accordance with annual guidelines. Due to seasonal variability in influenza activity and subtype prevalence, it is recognized that viruses may not be available to meet all specimen submission guidelines year-round. In addition, specific data and virus needs for annual vaccine virus selection and vaccine candidate development may necessitate adjustment to submission requirements as the season progresses. CDC may need to oversample specific subtypes/lineages to ensure their ability to identify appropriate candidate vaccine viruses.

Special considerations for Influenza A(H3) Viruses: Influenza A(H3) viruses undergo changes that require vaccine component updates more frequently than influenza A(H1) and B viruses. In addition, currently circulating A(H3) viruses have poor growth properties in eggs, a step necessary for the production of candidate vaccine viruses for most influenza vaccines. Therefore, while a detection threshold of 3% is still appropriate for A(H3) viruses, additional viruses are needed at CDC to assure timely production of vaccine candidate viruses. The resulting threshold is 95% confidence for the detection and growth of one candidate vaccine virus representing a particular drift variant at 10% prevalence among H3 viruses in the United States. In order to meet this goal, we assume that we have a three-month time period, PHLs will submit every 2 weeks, and there is a 4% chance of successful growth in eggs.

Objective: Antiviral Resistance Detection

National Threshold	Detection of antiviral resistance at or below 5% prevalence (one in 20 influenza positive specimens) among each influenza A subtype or influenza B lineage tested at the national level on a monthly basis.
Specimen Considerations	The same specimens submitted to CDC and/or NIRCs for vaccine virus selection are used to achieve this goal. If vaccine virus selection goals are met, this goal will also be met.
Rationale	This is the threshold at which CDC would consider issuing updated treatment guidelines to clinicians.

Objective: Situational Awareness for Seasonal Influenza

National Threshold	• Determine the percent of flu positivity among respiratory specimens with 95% confidence and a 5% margin of error. • To detect the start of influenza season, 137 unscreened respiratory specimens should be tested at either PHLs or clinical laboratories. To be confident in percent positivity around the peak of influenza season, 325 specimens should be tested on a weekly basis.
Specimen Considerations	This goal can be met by using clinical laboratory testing data (requires reporting of both positive and negative results) and data from PHLs derived from testing unscreened respiratory specimens. The data from samples tested in clinical laboratories can make up the majority, or even all, of the data used to meet this goal. Given the current level of physician ordered influenza testing, most jurisdictions should be able to easily meet or exceed the thresholds with data from only a small number of clinical laboratories which may be available through NREVSS.
Rationale	The sample size range among differing populations is minimal and there is an abundance of clinical lab data making the goal for the largest state achievable for all states so that was set as a minimum for all.* This goal requires less precision.

* The sample sizes for the start of season were set using the state with the largest population, California, and an assumption of 10% positivity and 2.2% ILI. For peak of season, goals were set using an assumption of 5% ILI and 30% positivity. The sample size goals are approximate goals so slight variations in these assumptions should not affect jurisdiction's sampling practices.

SAMPLING REQUIREMENTS AND IMPLEMENTATION GUIDANCE

Sampling Requirements

Influenza programs and public health laboratories should:

1. Have a network of providers and clinical labs to ensure timely flow of high-quality specimens throughout the year. These specimens should be representative of:
    - Virus types and subtypes/lineages
    - The entire year
    - Geographic diversity of the population
    - Age of patients
    - Disease severity (hospitalized vs outpatient)
    - Targeted populations when necessary for specific investigations
2. Meet minimum sampling requirements to meet national surveillance objectives. (Refer to your state's recommended sample size in Appendix A)
3. Send representative clinical specimens to CDC or NIRC laboratory for national surveillance purposes based on annual CDC/APHL criteria and guidance
4. Identify and resolve unsubtypable influenza positive specimens from any laboratory in your jurisdiction that performs subtype testing

CDC, at the national level, should:

1. Actively monitor laboratory testing data feeds and specimen submissions and as needed, solicit specimens, to meet minimum sampling requirements for national surveillance objectives
2. Ensure antigenic and genetic characterization is performed on a sufficient number of specimens to meet specification requirements
3. Provide guidance and support, as needed, in determining appropriate sample sizes for outbreak and novel virus situations

Build a Virologic Surveillance System

An adequate number of specimens should be tested to provide reliable data to meet the surveillance objectives at the thresholds outlined above. To build an effective virologic system at the jurisdictional level and to support national surveillance goals, public health laboratories and health departments need to work together to:

1. Establish a specimen and data provider network
2. Solicit specimens in a systematic manner
3. Report results

Routine influenza surveillance provides data and specimens to PHLs to achieve surveillance goals as determined by Right Size objectives and thresholds. Efficiency can be achieved by using a sampling strategy that provides sufficient specimens to address multiple surveillance objectives when possible. At a minimum, the virologic surveillance system in any PHL should be sized to achieve national novel virus and vaccine virus selection thresholds. By scaling surveillance to these levels, other goals of surveillance, such as antiviral resistance detection, will be achieved. Situational awareness goals should be achievable at the state level with clinical laboratory data but can be supplemented with unscreened respiratory specimens tested at the PHL.

The primary goals of influenza virologic surveillance are to:

- Detect novel influenza viruses
- Monitor circulating viruses for antiviral resistance
- Provide viruses for the detection of antigenic and genetic drift to inform vaccine virus selection and allow for vaccine candidate virus development
- Provide broad situational awareness of domestic influenza activity

Establish Data and Specimen Submitter Networks

Influenza testing occurs in a variety of settings including physician office laboratories, ambulatory care settings, hospital and commercial laboratories, and state, local and territorial PHLs. Data from influenza test results from these groups all contribute to state, local and territorial influenza surveillance systems as well as the US national influenza surveillance system. This complex virologic surveillance landscape can be summarized in **Figure 1**, with a more detailed specimen and data flow chart provided in **Appendix B**.

Influenza testing data and test specimens at the PHL should be obtained from:

- Healthcare providers (such as ILINet providers and other outpatient providers) who commit to regularly sending specimens collected from a subset of ILI patients that are not screened positive (or if screened, a random mix irrespective of test results) to PHLs for testing
- Clinical or commercial laboratories that submit specimens, either a mix of positives and negatives or influenza positives. If influenza positives only are submitted, they should be selected randomly regardless of virus type or subtype. Additionally, data on all influenza tests performed at clinical laboratories can be used to achieve situational awareness goals

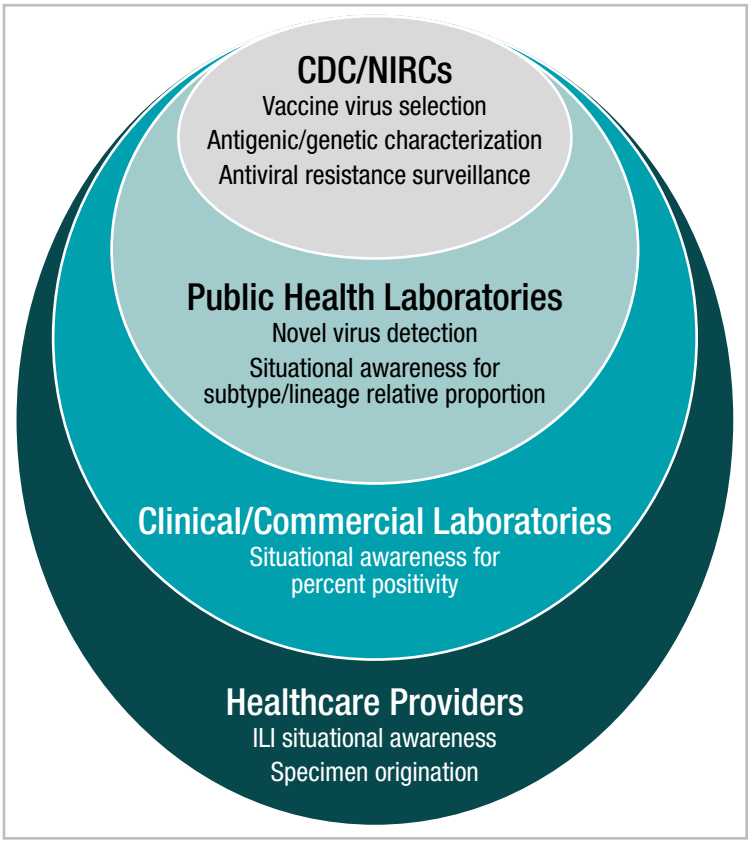

Figure 1. The US influenza virologic surveillance system is a tiered system. The same specimens answer various clinical and surveillance questions throughout the system with only a subset of specimens advancing to each subsequent level.

Identify Data Providers for Situational Awareness

For situational awareness, jurisdictions can use data from clinical and commercial laboratories to meet sample size goals. These data can be supplemented with unscreened, respiratory specimens tested at the PHL, but it is not a requirement that the specimens for this goal be tested at the PHL. Data from clinical and commercial laboratories participating in national surveillance can be accessed via NREVSS. To get more representative data from different patient populations, jurisdictions may also consider getting situational awareness data from outpatient providers (such as ILINet providers). One way to get provider data can be to gain access to point of care rapid tests via cloud reporting systems.

Recruit and Retain Specimen Providers for Novel Virus and Antiviral Resistance Detection and Vaccine Virus Selection

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 ensure specimens are representative of the population, including demographic variables such as age, geographic location, and healthcare setting. Ideally, the surveillance program should have the capability to establish targeted surveillance of specific populations if needed. Targeted surveillance (e.g., outbreaks, animal exposure, travelers outside the United States) may be useful to answer specific questions, especially if a novel influenza virus is detected. Your network should include:

- **Outpatient healthcare providers, such as ILINet participants**

  Outpatient facilities provide data and specimens for the influenza surveillance system. Specimen submitters may be ILINet sites or other outpatient healthcare providers. The selected specimen submitters should be committed to collecting high quality specimens and submitting the requested number of samples in a timely manner in accordance with jurisdictional criteria, throughout the entire year.

  ILINet and other outpatient healthcare providers may elect to test specimens using a point of care test (such as a RIDT). Specimens selected for submission to the PHL based on RIDT results (positives only or a mix or positives and negatives) can provide the submitting site with valuable information on the performance of their RIDTs. These samples, when tested in the PHL with the CDC Flu rRT-PCR Dx Panel, can be used to meet novel virus detection goals. Samples collected systematically from patients meeting the ILI case definition (fever ≥ 100° F AND cough and/or sore throat), regardless of RIDT results, can provide additional information that can be used to meet situational awareness goals and to calculate the proportion of ILI due to influenza. In this case, it is important to have methods to differentiate the systematically collected samples from those not within the PHL's laboratory information management system. Outside of influenza season, when influenza activity is low, participating providers and clinical laboratories should submit all RIDT positives to the PHL in addition to unscreened samples from a subset of patients from ILINet or other outpatient providers. When investigating novel influenza virus infections or increases in antiviral resistance, oversampling screened positives may be appropriate if the tests used are high performing with demonstrated reliability for detection of the virus of interest.

- **Clinical and commercial laboratories**

  In addition to the outpatient provider network, virologic surveillance should include specimens from hospital/clinical laboratories. PHL staff and/or the influenza coordinator should work with hospital laboratory staff to identify and solicit specimens that are from patients who exhibit severe respiratory illness (inpatients, for example). Many clinical laboratories also serve as reference laboratories for outpatient satellite clinics and therefore may be a good source of specimens for routine surveillance. The influenza surveillance coordinator, in collaboration with the PHL, should establish mechanisms to ensure submission of all unsubtypable influenza positive specimens from hospital/clinical laboratories performing influenza subtyping tests. If clinical laboratories are the primary resource for surveillance specimens, work closely with hospital laboratory staff to ensure that specimens submitted are representative of both outpatient and inpatient cohorts. Specimens from clinical laboratories should include both influenza positive and negative samples when possible. PHL testing of negative specimens will be useful to monitor the performance of test methods used in clinical laboratories.

- **Long-term care facilities or other institutional settings**

  Long-term care facilities (LTCFs) may need assistance with identifying the cause of respiratory disease outbreaks and can serve as a source of outbreak related specimens. Partnering with infection control staff at LTCFs prior to the start of the influenza season is recommended so that specimen collection instructions, specimen collection materials, and transport guidance are in place prior to the start of influenza activity. Influenza outbreaks at other institutional facilities such as childcare facilities, correctional facilities, shelters, or other settings could also be sources of outbreak related specimens and for which healthcare providers may need additional type/subtype/lineage information for control efforts.

- **Medical examiner's office**

  Partnering with the medical examiner's office enables access to samples from influenza related deaths. Laboratory confirmed influenza-associated pediatric deaths are a nationally notifiable condition, therefore, specimens tested at a public health lab can be critical in the identification of these cases. Testing specimens from adults whose death is suspected or identified through rapid influenza diagnostic testing or other test methods, to be associated with influenza disease can provide additional information on the specific virus involved in these severe outcomes and may help inform influenza prevention and control measures.

- **Federally Qualified Health Centers**

  Federally Qualified Health Centers are community-based healthcare providers that receive funds from the HRSA Health Center Program[4] to provide primary care services in underserved areas. These centers may include Community Health Centers, Migrant Health Centers, Healthcare for the Homeless, and Health Centers for Residents of Public Housing.

Solicit Specimens in a Systematic Manner

Source of Specimens

The number of samples required to meet situational awareness and novel virus detection objectives will vary by health department based on the population of the jurisdiction. Efficiency can be achieved by using existing data and a sampling strategy that allows specimens to address multiple surveillance objectives, for example:

- Situational awareness goals may be achieved in large part using test result data reported from clinical laboratories.
- A subset of influenza positive samples from the clinical laboratories can be submitted to the PHL, where they can be tested to meet novel influenza virus detection goals.
- A subset of samples positive for seasonal influenza in the PHL can be forwarded to CDC or a NIRC for antiviral resistance testing and genetic and antigenic characterization to inform vaccine virus selection and vaccine candidate virus development

Sample size calculations are based on population size, desired level of confidence, margin of error, and estimated or known prevalence or threshold for detection in order to achieve a more scientific, statistically based sample size that supports surveillance objectives. Some jurisdictions, particularly those with smaller populations, will likely need to exceed the testing goals set for novel influenza virus detection in order to achieve overall situational awareness for the local influenza season. Additionally, if a jurisdiction participates in other components of surveillance such as the national system for laboratory-confirmed influenza-associated hospitalizations (FluSurv-NET), more specimens may need to be tested than the number required to meet Right Size goals outlined in this document.

During times of little or no influenza virus circulation, the number of results needed from specimens tested for influenza to achieve the desired statistical confidence will not be achievable in most jurisdictions. Therefore, the focus of surveillance should shift to obtaining specimens from clinical sites that have tested positive for influenza, or from patients with unusual respiratory illness, travel history, risk of exposure to animal-origin viruses, or other characteristics of interest.

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

- Targeted or increased surveillance may be needed at times to answer specific questions. Examples include:
- Investigation of novel influenza virus infections
- Looking for cases of novel influenza virus infections in travelers from areas where novel influenza viruses are circulating
- Following up on clusters of infections with viruses resistant to antiviral medications

Therefore, the surveillance program should have the flexibility and capability to establish targeted surveillance of specific populations when needed and the capacity to perform testing on specimens from these patients. CDC will provide guidance to state epidemiologists, influenza surveillance coordinators and PHLs on the specific risk factors and need for enhanced surveillance (e.g., exposure to avian influenza viruses or swine exposure).

Frequency of Specimen Submission

Outpatient Provider and Clinical Laboratory Specimen Submissions to PHLs

The frequency of specimen submission for routine surveillance will vary depending on jurisdictional needs and PHL capacity for specimen intake and processing. During the influenza season, it may be most convenient to ask providers to send specimens from the first few ILI patients they see each week. If the PHL prefers to receive specimens throughout the week, each provider may be asked to collect and send specimens on a different day. Specimens need to be submitted and tested in real time—not batched—in order to provide situational awareness, inform timely clinical management guidelines, and ensure rapid detection of novel or antiviral resistant viruses. If specimens are sent to the PHL for diagnostic testing (e.g., patient with high-risk travel history, or unusual case presentation), they should be transported promptly—not batched with surveillance specimens—and should be tested as soon as possible in the PHL. Clinical laboratories that perform PCR testing

with subtyping should immediately submit any specimens that produce unsubtypable test results to the PHL. Conversely, clinical laboratories should be notified of the most recent epidemiologic criteria for a potential case of human infection with a novel influenza virus.

Provider compliance with specimen submission criteria may be enhanced by providing:

- Clear instructions and submission forms customized for their site
- Cost-free specimen collection kits and shipping
- Guidance for optimum specimen collection
- Feedback and data to submitters, including influenza test results and/or results of testing for other respiratory pathogens if performed
- Annual, or as feasible, site visits to providers to build relationships, explain importance and value of participation and discuss submission guidance
- No cost training
- Certificates of recognition
- Other incentives such as RIDT kits

PHL Submission to CDC and National Influenza Reference Centers (NIRCs)

All state and some local and territorial PHLs perform rRT-PCR testing to type and subtype/lineage genotype influenza viruses in clinical specimens using the CDC Flu rRT-PCR Dx Panel. Every PHL participating in virologic surveillance is responsible for testing clinical specimens for surveillance purposes or epidemiologic investigations and reporting data to CDC in a timely manner. CDC strongly recommends that PHLs subtype all influenza A positives and perform lineage testing on all influenza B viruses to help meet novel virus detection goals and provide critical data to enhance all aspects of influenza surveillance. Large state health departments should consider collaboration with local health departments performing the CDC rRT-PCR test in order to collectively achieve novel virus detection goals.

Unsubtypable specimens require immediate action as they may reflect a novel virus with pandemic potential.[5] CDC must be notified immediately, and these specimens must be sent to CDC as soon as possible for comprehensive testing.

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PHLs are also required to submit representative clinical specimens to their assigned NIRC for national surveillance purposes. NIRCs provide advanced testing on behalf of CDC for national surveillance. Laboratories should submit specimens in a timely manner based on annual CDC specimen submission guidance distributed via APHL. To enhance CDC's vaccine virus selection efforts, it is important to send recently collected specimens (i.e., typically the past two weeks since previous shipment). Specimens submitted to CDC should be representative of the geography, disease severity, and patient age of the population and for each circulating influenza A virus subtype and influenza B lineage. Oversampling of low prevalence subtypes/lineages is necessary to ensure that all circulating subtypes and lineages are represented. When virus circulation levels allow, the number of specimens from each subtype/lineage submitted to CDC should be roughly equal, meeting the vaccine virus selection thresholds and giving the same likelihood of detecting a drifted virus within each subtype/lineage (**Figure 2**). Viruses from particularly severe or unusual cases and a subset of specimens from outbreak investigations can be included in submissions to CDC and NIRCs. CDC may request additional viruses/specimens depending on circulating virus trends, vaccine virus selection, and vaccine candidate development needs. When choosing specimens that meet the requested submission guidance, laboratories should preferentially include specimens that have additional epidemiologic data available.

Recognizing and Addressing Sources of Bias

The influenza virologic surveillance system contains inherent biases due to the complexity of the sampling and submission processes and the use of different test methods in different testing settings. Sources of bias should be considered and addressed, if possible, when selecting specimen providers, test methods, and sample submission protocols when analyzing and interpreting data.

Bias can be introduced both unintentionally and intentionally. Intentional bias occurs when we specifically solicit samples from groups with specific exposures, characteristics, and courses of illness, as well as through the use of screened positive samples for testing in PHLs. It is important to understand where data may be biased and look for the most appropriate way to analyze data so that bias can, to the extent possible, be accounted for. Here are some common sources of bias which are critical to recognize and address either in data analysis and interpretation or by changing how specimens are solicited:

- **Test sensitivity**
  Depending on the goals of the surveillance program, test sensitivity can have impacts in different ways. If the program's primary goal is to determine the percent of patients with influenza-like illness (ILI) that test positive for influenza, then a test with high sensitivity and specificity (i.e., a molecular test) should be used, and the specimens tested should be collected from patients who meet the ILI case definition. If the program's goal is to simply follow trends and the percent of ILI that is attributed to influenza is not of importance, then consistency in test methodology is the most important factor. Also, RIDTs may have differing sensitivity and specificity by virus type/subtype, and that can bias data on the relative proportions of viruses detected. If influenza positive specimens reported from a surveillance site or clinical laboratory are used as the pool to solicit samples for further testing in the PHL, then this differing sensitivity/specificity depending on the test methodology used at the site can introduce bias into specimens coming into the PHL.

- **Specimen Providers**
  Specimen providers should seek to represent the entire population under surveillance. Choose a mix of providers representing all patient age groups (pediatrics, family practice, internal medicine, and geriatrics) and the spectrum of disease severity. Specimen providers should also be selected to represent areas of diverse population density (urban, suburban and rural), and racial and ethnic groups.

- **Unscreened vs. Screened Influenza Positive Specimens**
  Both types of specimens can be useful in influenza virologic surveillance, but it is critical to understand when to use which data. Therefore, these sources of data must be able to be differentiated within the data management tools of the PHL. If submitters are using RIDTs for diagnostic purposes, a random mix of RIDT specimens—irrespective of RIDT results—should be submitted to the PHL for surveillance purposes.

  If screened specimens from clinical laboratories are the primary source of surveillance specimens, these may be overly representative of hospitalized patients (which usually bias toward severe cases) or may only represent specific facilities or geographic areas within the jurisdiction. Data may not be representative of true prevalence of virus subtypes in the general community. This bias may be mitigated by selecting sites that can provide specimens from both emergency room and inpatient settings in all areas of the jurisdiction and providing clear guidance on numbers and types of specimens to be submitted.

Report Results

The final step in establishing and maintaining an effective virologic surveillance system is reporting results back to submitters at all levels and to the public and other stakeholders as appropriate. This is an essential function of laboratories and surveillance programs at all levels of the surveillance system. In order to effectively report results that meet the needs of each stakeholder, appropriate data management systems and practices must be in place. Please refer to the "Data Management" section for more information on establishing data management practices that meet the needs of the US influenza virologic surveillance system.

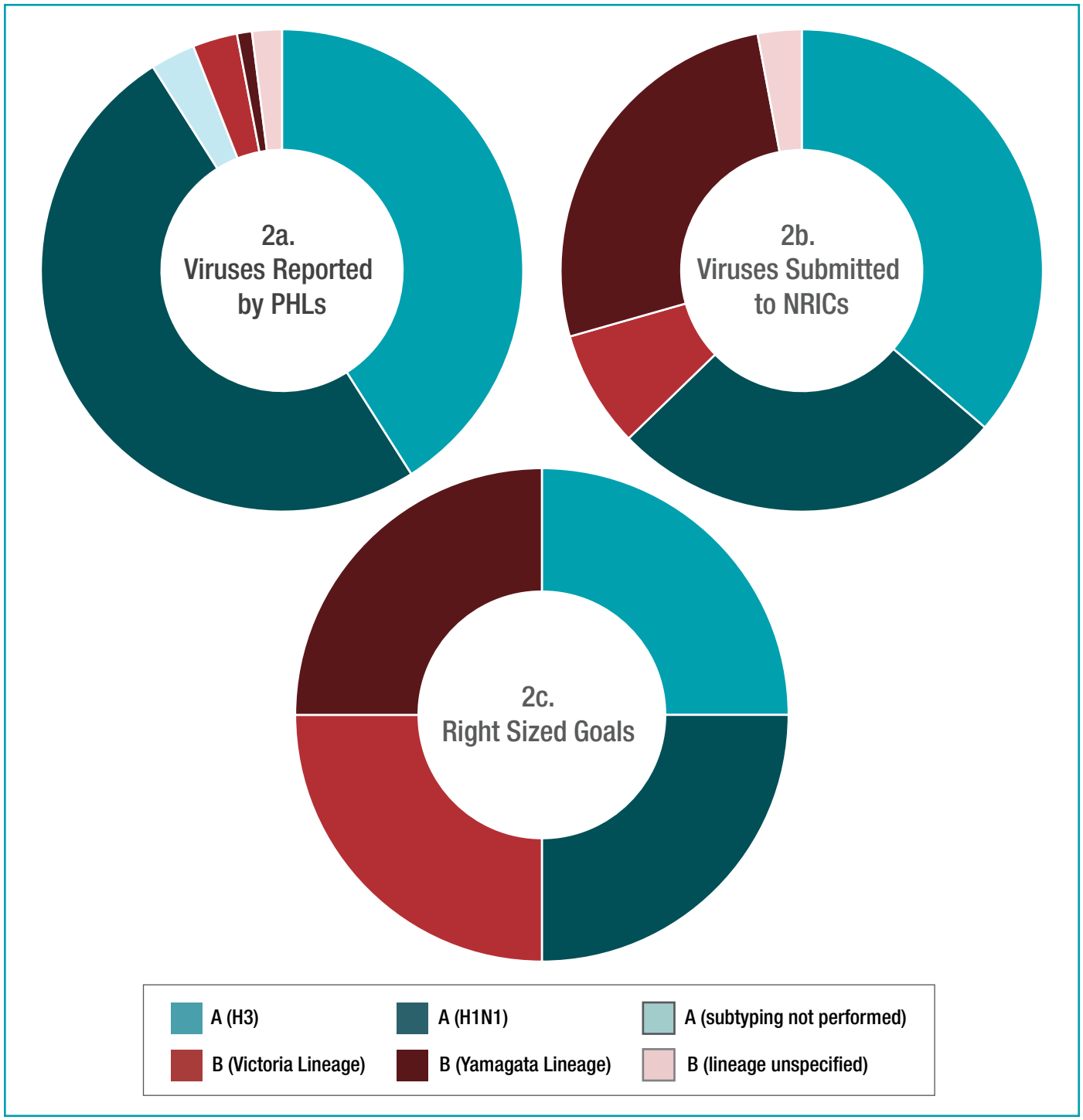


Figure 2. Right Size guidance aims to oversample the less prevalent viruses and limit unnecessary testing of the predominant viruses. This is to achieve efficiencies and to increase data confidence for less predominant viruses when making vaccine virus decisions.

- **Figure 2a** shows real data reported to CDC by PHLs during the 2018-2019 season for the week ending September 28, 2019 showing the true relative proportions of circulating viruses.
- **Figure 2b** shows how Right Size specimen submission guidance aims to oversample the less prevalent subtypes but how real-world circulation affects our ability to meet our true goal.
- **Figure 2c** shows the ultimate Right Size goal, which is likely not achievable due to fluctuations in co-circulation of different subtypes/lineages.

LABORATORY TESTING REQUIREMENTS AND IMPLEMENTATION GUIDANCE

Laboratory Testing Requirements

Influenza programs and public health laboratories should:

1. Detect, type and subtype/lineage influenza viruses from clinical specimens in a timely manner using reliable laboratory methods.
2. Use molecular detection and subtyping methods (e.g., rRT-PCR) for influenza virologic surveillance.
3. Maintain instrumentation, personnel, expertise, and adequate capacity to test the volume of specimens needed to achieve national and jurisdictional surveillance objectives.
4. 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.
5. Notify CDC immediately and ship unsubtypable influenza A viruses to CDC within 24 hours of detection to confirm or rule-out novel viruses.
6. Routinely refer a representative subset of specimens to CDC and NIRCs for genetic and antigenic characterization.
7. Maintain capability to rapidly adopt new test methods or test modifications if a new influenza virus with pandemic potential emerges or when new technology provides improvements to virologic surveillance.
8. Maintain additional influenza testing capabilities (as defined in this document) as appropriate for the jurisdiction or use regional consortium agreements to ensure access to testing.

CDC, at the national level, should:

1. Identify, characterize, and rapidly conduct risk assessments of seasonal and emerging novel influenza viruses.
2. Develop, deploy, and evaluate CDC assays to assure optimum performance.
3. Optimize sequencing methods; evaluate new technologies.
4. Develop technical standards and guidance for virologic surveillance.

Laboratory Testing Requirements Rationale

By definition, influenza virologic surveillance 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 take 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.

The Roadmap classifies virologic testing components into:

1. **Required testing:** requirements that should be maintained and available at all PHLs involved in influenza surveillance.
2. **Optional enhanced testing:** additional surveillance testing capabilities that may be maintained based on jurisdictional needs and resources or provided through a regional consortium.

Required Test Method

PHLs performing virologic surveillance are expected to use the CDC Flu rRT-PCR Dx Panel for influenza detection and subtyping. This is also an ELC benchmark. The CDC Flu rRT-PCR Dx Panel provides rapid, sensitive, and accurate detection and identification of influenza viruses for routine influenza surveillance, outbreak detection, and pandemic response.[5,6]

During rRT-PCR test processes, viral RNA is extracted from patient specimens, transcribed into DNA and amplified. The product of the test reaction is detected in "real-time" using labeled probes. Real-time RT-PCR can rapidly identify influenza A and B viruses, distinguish between influenza A subtypes and B lineages, and offers the best performance characteristics (i.e., sensitivity, specificity) of all currently available testing methods. 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, through the International Reagent Resource (IRR), to all qualified state and local PHLs engaged in influenza virologic surveillance testing. 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, but may not identify, novel influenza A viruses. The assay also allows for higher throughput testing algorithms to support outbreak and pandemic responses.

The PHL is responsible for the timely referral of representative specimens to CDC or a NIRC for genetic, antiviral and antigenic characterization throughout the year in accordance with annual submission guidance distributed by APHL.[7] To enhance CDC's vaccine virus selection efforts, it is important to routinely and consistently send recently collected specimens.

Optional Enhanced Testing Methods

There are additional testing methods that may be used to support influenza virologic surveillance. These include antiviral resistance testing of influenza viruses, respiratory pathogen panels, next generation sequencing and CLIA-waived devices (antigen detection and nucleic acid amplification tests [NAAT]). 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 based on state and jurisdictional needs, detailed cost analysis and identification of a sustainable funding source(s) (see Financial Resources section). Financial support for these test methods is most likely to be only partially available or not available at all at the federal level, and these methods are therefore not required to meet national surveillance needs.

Respiratory Pathogen Panels

Testing for other respiratory viruses using molecular respiratory pathogen panels (RPPs) is common in many clinical laboratories and PHLs to provide 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 providing a more complete picture of respiratory activity. If surveillance for other respiratory viruses is performed to meet jurisdictional needs and resources are available, it is recommended that PHLs consider adopting molecular RPPs to replace less sensitive viral culture. Results from molecular RPPs can be reported via NREVSS to CDC, contributing to national surveillance for influenza and other respiratory pathogens.

Antiviral Resistance Testing

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 and detection of genetic markers associated with drug resistance. Both of these test methods are performed at CDC and NIRCs to meet national antiviral resistance detection surveillance goals. CDC also offers antiviral resistance detection testing to aid in patient management in cases of clinical suspicion of antiviral resistance. To meet national right size goals for detecting the emergence of resistant viruses, it is sufficient to support these methods at CDC and the NIRCs though other PHLs may choose to support the testing on their own specimens for their jurisdiction's purposes.

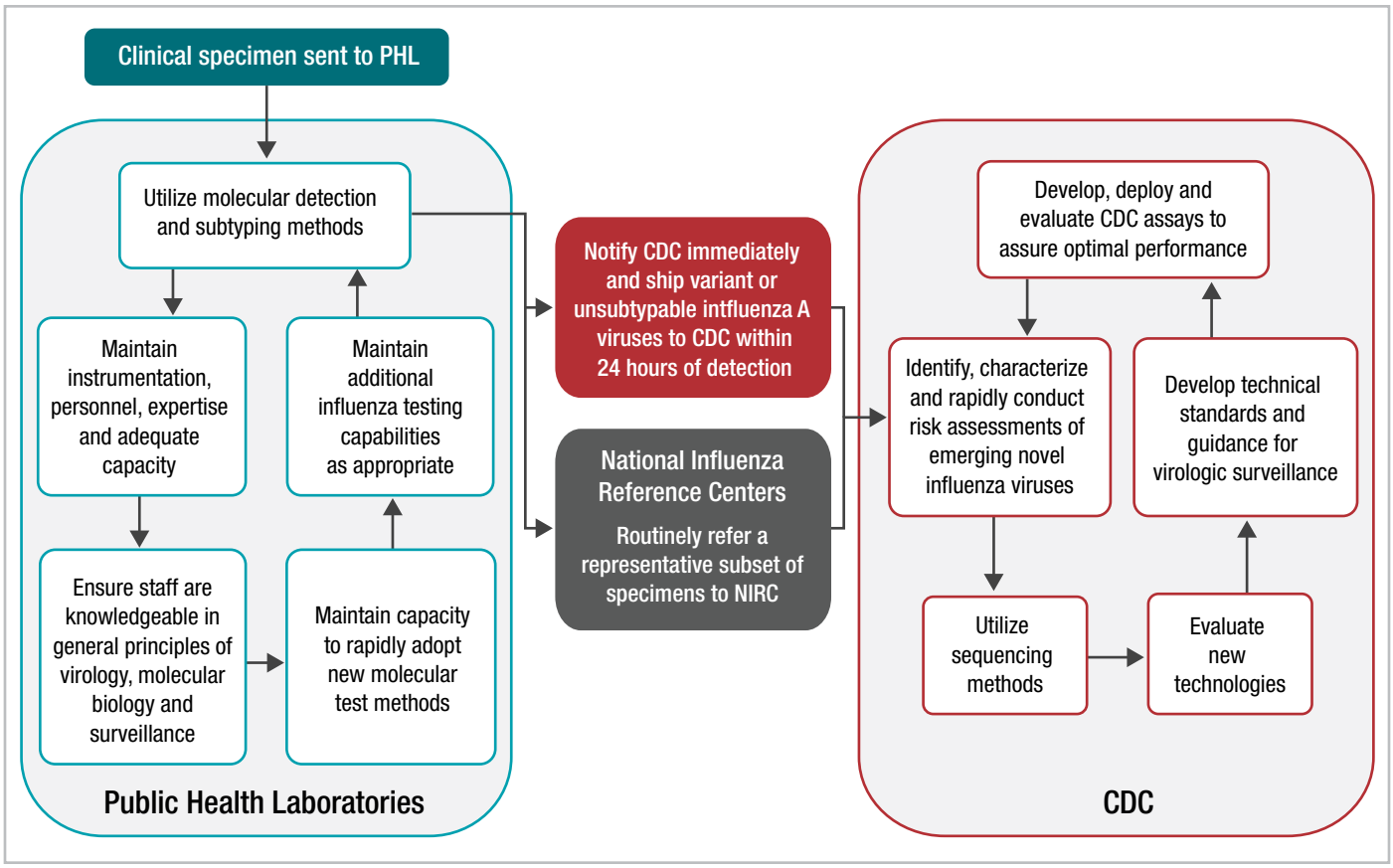


Figure 3. Roles and responsibilities for laboratory testing in the US influenza virologic surveillance system.

CLIA-waived devices (RIDT and NAAT)

Many sentinel surveillance providers, other outpatient sites and emergency departments, physician offices, and clinical laboratories use CLIA-waived devices for fast, near point-of-care diagnostics. CLIA-waived tests are not subject to stringent CLIA quality standards, including routine inspections, quality control beyond measures outlined in the package insert, proficiency testing, and personnel requirements.[8] These CLIA-waived devices include:

- Traditional or first generation visual-read RIDT test systems (antigen detection-based method)
- Newer generation waived instrument-read RIDT test systems (antigen detection-based method)
- Waived molecular tests

Currently available RIDTs for the detection of influenza viruses employ a variety of methods, including enzyme-linked immunosorbent assays, immunochromatographic lateral flow immunoassays and membrane-based immunoassays. However, these tests are significantly less sensitive and specific than molecular assays.[9,10] RIDTs may also be less reliable when new viruses emerge.

While RIDTs can play an important role in serving diagnostic needs for selected patient populations, they do have limitations (e.g., the considerable variability of the positive and negative predictive values depending upon the prevalence of influenza in the community) and users should follow guidelines provided by CDC.[11] 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. In 2017, FDA published a final order to reclassify RIDTs from Class I to Class II devices with special controls. The hope is that this order will improve the performance of RIDTs that remain on the market; it is important to note that this order only applies to antigen-based RIDTs.[12]

Similarly, while waived molecular tests may be more sensitive, they also have limitations such as potential for nucleic acid contamination and have been subject to false positive and negative values as well.

Virology staff should maintain awareness of the performance characteristics of currently available CLIA-waived devices that may be used within their jurisdiction in order to provide seasonal guidance to clinicians, clinical laboratories and surveillance coordinators. APHL also published Communication Points for Public Health Laboratories Regarding CLIA-waived Influenza Diagnostic Tests[13] to assist with guidance.

Next Generation Sequencing (NGS)

Advancements in gene sequencing technologies (e.g., NGS) have allowed PHLs to rapidly perform genomic sequencing for influenza viruses direct from clinical specimens.[14] NGS technology was deployed to NIRCs in 2015-2016 to further strengthen influenza surveillance nationally. There are numerous benefits of rapidly sequencing influenza viruses including:

- Situational awareness and timely recognition of emerging variant viruses.
- Monitoring influenza virus evolution in near real-time.
- Rapidly detect genetic changes that are associated with antiviral resistance.
- Outbreak characterization and transmission dynamics.
- Sharing sequence data in public databases (e.g., GISAID and NCBI) for researchers around the world to access.
- Development of a "sequence first" approach to improve efficiency of the subset of influenza viruses that undergo antigenic characterization.
- Testing clinical specimens directly shows what the virus looks like in the host and mitigates cell culture adaptations.

While jurisdictions may have a desire to sequence specimens for special studies and outbreak investigations, there is not a national need to expand sequencing capacity to all states. The specimens submitted by PHLs and sequenced at the NIRCs following Right Size submission guidance is sufficient to meet national surveillance goals. Sequence accessioning information is made available by CDC to PHLs so laboratories can access curated sequences from their specimen submissions via public database such as NCBI's GenBank[15] and GISAID.[16] Jurisdictions may have other reasons for implementing influenza sequencing beyond the specimens submitted for national surveillance.

Considerations for Maintaining or Implementing NGS for Influenza

The following questions can be used as a decision tool in deliberations among the laboratory director, senior infectious disease laboratory staff, epidemiologists, influenza surveillance coordinator and clinical laboratory partners when deciding if NGS is worth pursuing in your laboratory for influenza viruses.

1. How do you intend to use NGS data? Will these results be available to individual patients and providers (CLIA implications apply)? What will results look like and will they need interpretation? How will the information from NGS inform public health actions? Is NGS data the most cost-effective method to get this information or can you get it from other data sources (e.g., PCR)?
2. Can you glean sufficient information from the sequences deposited in GenBank and GISAID by CDC and NIRCs? (Sequence reference numbers are provided on CDC's reporting portal)
3. Do you currently have support to refer specimens for NGS to other local, state or regional partners?
4. Does your need for NGS referral meet or exceed the capacity of the referral laboratory?
5. Are there specific questions that could be answered using NGS that would enhance your understanding of particular infectious disease situations in your state?
6. Do you have dedicated staff sustainably employed and trained to conduct NGS?
7. Do you have staff experienced with bioinformatics or access to external bioinformaticians?
8. What protocols will you use for influenza NGS? Will you need support, training, and protocols from the CDC? Upon implementation, would your laboratory be interested in hosting regional trainings for other laboratories?
9. Is there consistent funding for sequencing reagents, maintenance contracts for sequencers and ancillary equipment?
10. Does your laboratory have the capacity to store high volume sequencing data (e.g., extra servers, cloud-based applications, backups, etc.)?
11. Have you considered data use agreements with providers for disclosing how human genetic information will be evaluated, stored, and protected?
12. Which testing programs, if any, would NGS replace in your laboratory and what affects could this have on your provider/patient population?

DATA MANAGEMENT REQUIREMENTS AND IMPLEMENTATION GUIDANCE

Data Management Requirements

Influenza programs and public health laboratories should:

1. Ensure that all databases and transmission networks are secure
2. Report results to providers, epidemiologists, and CDC
3. Use electronic data systems that provide data to CDC in (near) real-time and use national standards (HL7, SNOMED and LOINC)
4. Maintain the ability to rapidly modify messages as needed in an emergency response (i.e., add a novel virus)
5. Include the following data elements in reports to CDC:

Required:

- Specimen identifier
- Unique patient identifier
- Jurisdiction where the specimen was collected
- ID number if the submitter is part of a CDC Program (e.g., ILINet provider, FluSurv-NET, other)
- Date of birth of the patient and/or age with unit (years, weeks, months, days)
- Race/ethnicity
- Specimen collection date
- Specimen receipt date
- Specimen type
- Test method performed
- Test result

If Available:

- Gender
- Current influenza vaccination status
- Non-influenza respiratory virus test results
- Antiviral treatment
- Patient status at time of testing (inpatient, outpatient, long-term care facility)
- Travel information
- Patient death information
- Additional geographic information (e.g., county, city, zip)
- Whether specimen was related to an outbreak
- Whether specimen was sent to CDC and if so, include specimen identifier
- Date of illness onset
- Pre-screened test result
- Pregnancy status

6. Monitor and use clinical testing data to achieve situational awareness goals

CDC, at the national level, should:

1. Support and maintain infrastructure for standardized, electronic reporting of laboratory results and surveillance data
2. Provide updated mapping and encoding guidelines, as needed

Influenza Virologic Surveillance Data Landscape

Virologic surveillance in the United States relies on a combination of data and specimens. Data are reported from laboratory tests performed at public health and clinical laboratories in two different networks: the US World Health Organization (WHO) Collaborating Laboratories (WHO CLs) and National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories.[17] These data are reported as either specimen level data through HL7 messaging or comma delimited files, or aggregately through web-based reporting tools (**Figure 4**). A subset of specimens that test positive for influenza at PHLs are regularly forwarded to CDC, or to designated reference laboratories, for further testing including whole genome sequencing, antiviral resistance testing, and genetic and antigenic characterization to assess similarity between circulating influenza viruses and those viruses included in the seasonal influenza vaccine.

Health departments can access data from NREVSS reporters in their jurisdictions which can a valuable resource to help meet situational awareness goals. Contact nrevss@cdc.gov for questions.

You can report non-influenza respiratory testing results to NREVSS via PHLIP. Contact informatics.support@aphl.org.

As of 2019, there were approximately 100 WHO CLs in the United States, including 85 state, territorial and local PHLs supported by CDC, as well as laboratories in several large tertiary care or academic medical centers.[18] These laboratories have the capability to test for and report influenza type and subtype. These laboratories provide both data and specimens to CDC. NREVSS is managed by CDC's Division of Viral Diseases and is the main source of national laboratory surveillance data for non-influenza respiratory viruses, but influenza testing data collected in NREVSS are shared with CDC's Influenza Division.

Health departments can also access NREVSS data for reporters in their jurisdiction. NREVSS includes clinical, commercial, and academic medical center laboratories, as well as some PHLs. Most NREVSS laboratories that are not WHO CLs provide data on influenza laboratory test results by influenza virus type and, when available, subtype. The influenza data reported by the WHO collaborating laboratories and NREVSS laboratories are summarized in CDC's weekly influenza surveillance report, FluView.[19]

Additional influenza testing data from rapid influenza diagnostic testing sites and/or other clinical laboratories may be available to health departments and can help provide a fuller representation of influenza activity at the local level but are not included in national influenza surveillance reports. These clinical sites should have the capability to test for and report the type of influenza virus (A or B) identified in a specimen, but some also use methods that can subtype influenza A viruses.

Public Health Laboratory Data Management

The data generated through PHL reporting are published each week through CDC's FluView.[19] Therefore, timely and accurate reporting of laboratory surveillance data using electronic data systems is critical. Currently, influenza surveillance data are obtained as aggregated data using a web entry tool and as specimen level data using HL7[20] electronic laboratory reporting and comma delimited files (**Figure 4**). This mix of reporting methods with varying levels of detail makes the data management, aggregation, and linking of virologic and epidemiologic data challenging. However, the spectrum of reporting formats used reflects a long history of virologic surveillance with varying technological solutions and capabilities of reporters.

The increased technical capabilities and health information technology infrastructure in PHLs make it possible to establish automated electronic laboratory messaging of influenza test results to other public health entities (e.g., health department epidemiology offices, other PHLs, and CDC). The Public Health Laboratory Interoperability Project (PHLIP) provides PHLs with an electronic method to report individual laboratory test results to CDC using national electronic messaging standards such as HL7, SNOMED[21] vocabulary, and LOINC[22] codes for laboratory tests. PHLs can find information regarding implementation of HL7 messaging for CDC Flu rRT-PCR Dx Panel, including applicable LOINC test codes and SNOMED result codes from CDC's Guidance for Standards-Based Electronic Laboratory Reporting for Influenza.[23]

The PHLIP vision is to provide each PHL 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 as of 2022 all state PHLs are reporting influenza results electronically using PHLIP.

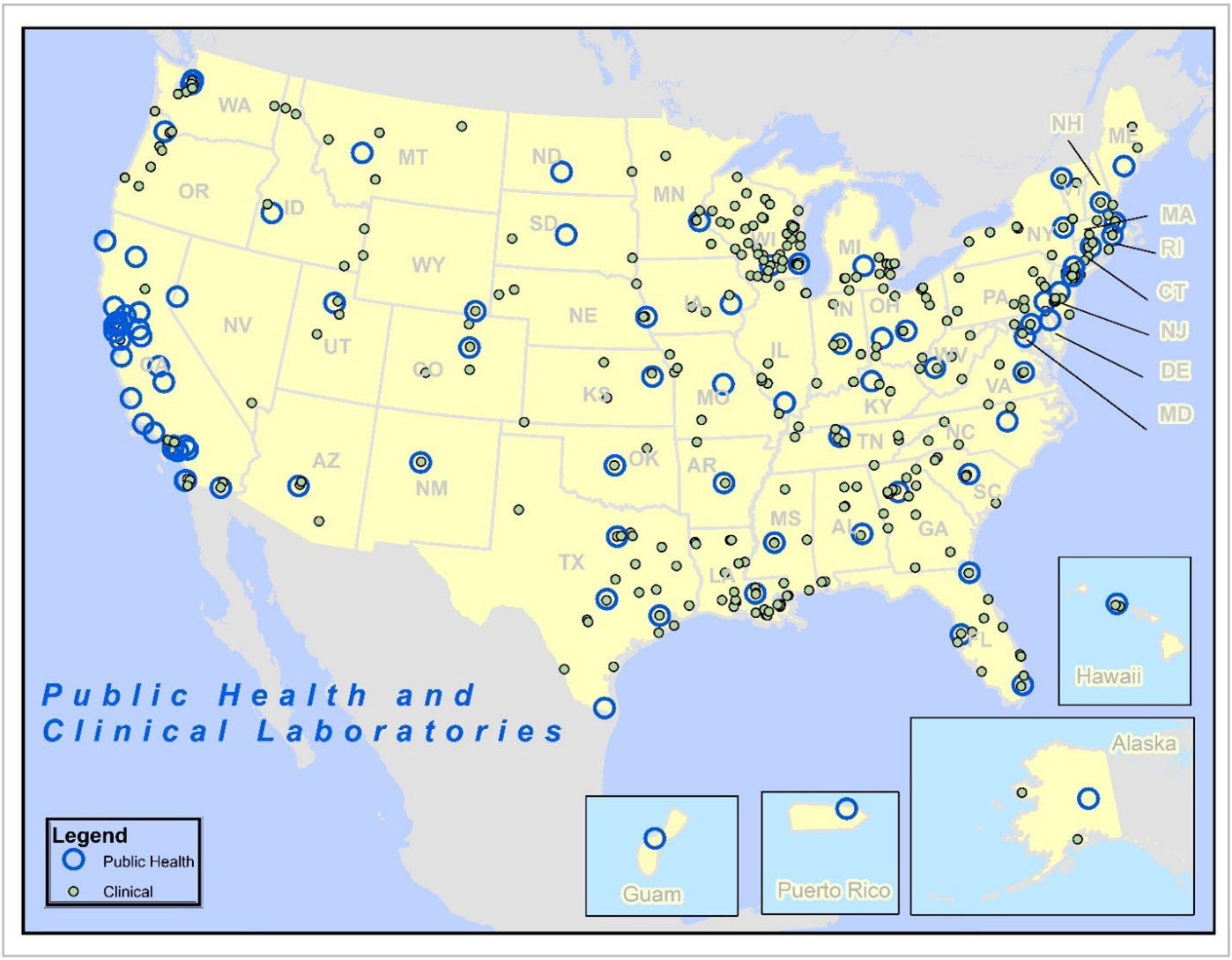


Figure 4. Representation of Public health and clinical laboratories across the United States, 2019 (Source: CDC Unpublished Data)

PHLIP is the preferred reporting mechanism to CDC for influenza and is considered a Right Size Influenza Virologic Surveillance requirement. PHLIP implementation should be the goal for all state and territorial PHLs and for county and local PHLs that participate in virologic surveillance. PHLs should use the current HL7 standard; as of 2021, the Right Size requirement is for PHLs to use HL7 Version 2.5.1 at a minimum. PHLIP offers many advantages, which include:

- Standardizes specimen 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, such as other respiratory viruses, using the same mechanisms for messaging
- Reduces laboratory staff time required to collect and report laboratory results
- Provides an option for additional information to be included in the message (e.g., ILINet provider ID, FluSurv-NET site ID, epidemiologic information, etc.) which is being used in enhanced surveillance projects

Virologic Surveillance Data from Non-PHL Sources

The focus of virologic surveillance in the United States has historically been on data generated by the PHLs participating as WHO CLs. However, influenza testing performed by clinical and commercial diagnostic laboratories provides useful supplementary data, increasing the overall volume of testing and geographic representation. For efficiency reasons, public health departments and laboratories are encouraged to explore options to collect and incorporate influenza testing data from non-PHL sources. These non-PHL sources of data can also be used to achieve Right Size seasonal influenza situational awareness goals. Existing virologic data from non-PHL sources, notably NREVSS, and some options for new sources of virologic data are discussed below.

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, or PCR) and 3) number of influenza positive specimens by influenza type and if available, by subtype and age group.

Additional sources of influenza clinical, hospital and/or commercial laboratory (NREVSS-like) data can also be used and developed. For the same reasons that NREVSS data are useful at the national level, laboratory networks in each jurisdiction can serve as a source of additional local level data. Data from these sites may be transmitted electronically at the specimen level or in aggregate by a simpler method. Large commercial laboratories (e.g., Quest Diagnostics, LabCorp, ARUP Laboratories and Mayo Medical Laboratories) could be a source of additional data.

A number of health departments have initiated laboratory test reporting from selected point-of-care testing sites and clinical laboratories in their jurisdiction. These data are used by the influenza surveillance coordinators to monitor influenza activity. Providing the supplemental surveillance data to clinicians is a useful resource to guide patient management decisions.

Considerations for Data Management

1. If currently utilizing PHLIP, what data elements are being sent? Have you explored incorporating the additional information fields listed above in the requirements section (i.e., “if available” fields)? Have you considered mapping other respiratory assays that can result in influenza (e.g., RPPs)?
2. Have you identified the potential sources of bias in your virologic surveillance data? What changes could be made in your system to reduce the impact of bias? What steps have been taken to ensure appropriate interpretation of the data given any existing bias?
3. Does your influenza surveillance system incorporate virologic data from clinical/commercial laboratories? If yes, how are these data collected from the laboratories? Are the number of positive tests and the total number of specimens tested (denominator data) reported? How stable and reliable are the data being received?
4. If no clinical/commercial lab data are currently collected and incorporated into your surveillance data, do you have plans to collect these data in the future? What are the challenges to collecting these data?
5. What is the plan for incorporating new data sources into your influenza surveillance data?
6. What resources are required to collect non-public health laboratory testing data?

PARTNERSHIPS AND COMMUNICATION REQUIREMENTS AND IMPLEMENTATION GUIDANCE

Partnerships and Communication Requirement

Influenza programs, public health laboratories and CDC should establish and maintain partnerships and communication networks which support routine influenza surveillance, data sharing, specimen sharing and can be used for emergency preparedness and response. These partnerships and communication networks are needed at various levels among and between public health and healthcare communities including:

- CDC
- Influenza surveillance coordinators
- State and territorial epidemiologists
- Public health laboratories
- Clinical laboratories
- Commercial laboratories

Key Partnerships for Effective Influenza Virologic Surveillance

The United States' 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*.[24]

The most important partnership for effective influenza virologic surveillance is the relationship between the PHL staff and epidemiology/influenza coordinators within state, local and territorial health departments. This partnership results in improved 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 understand each other's roles and agree 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. Strong partnerships among PHLs, epidemiologists and clinical/commercial/academic laboratories will support the formation of an effective specimen submitter network and enhance situational awareness and outbreak response. Strong relationships among epidemiology/influenza coordinators, PHL and clinical partners are crucial to ensuring high quality and consistent data and specimens for influenza virologic surveillance.

Gaps in effective partnerships can result in significant but often poorly-recognized negative impacts on virologic surveillance.

Additional key PHL relationships are outlined in several documents, including APHL's *Core Functions of Public Health Laboratories*,[25] *Definition of a State Public Health Laboratory System*[26] and CDC's *Public Health Preparedness Capabilities: National Standards for State and Local Planning*.[27] 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 APHL's Lab System Improvement Program[28] (L-SIP), All-hazards Public Health Emergency Preparedness (PHEP) initiatives,[29] the CDC/ Council of State and Territorial Epidemiologists (CSTE) Competencies for Applied Epidemiologists in Governmental Public Health Agencies[30] (AECs) and the Laboratory Response Network[31] (LRN) for years.

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 CDC, APHL, private industry, and others included in **Figure 5**. Similar relationships exist between CDC and influenza surveillance

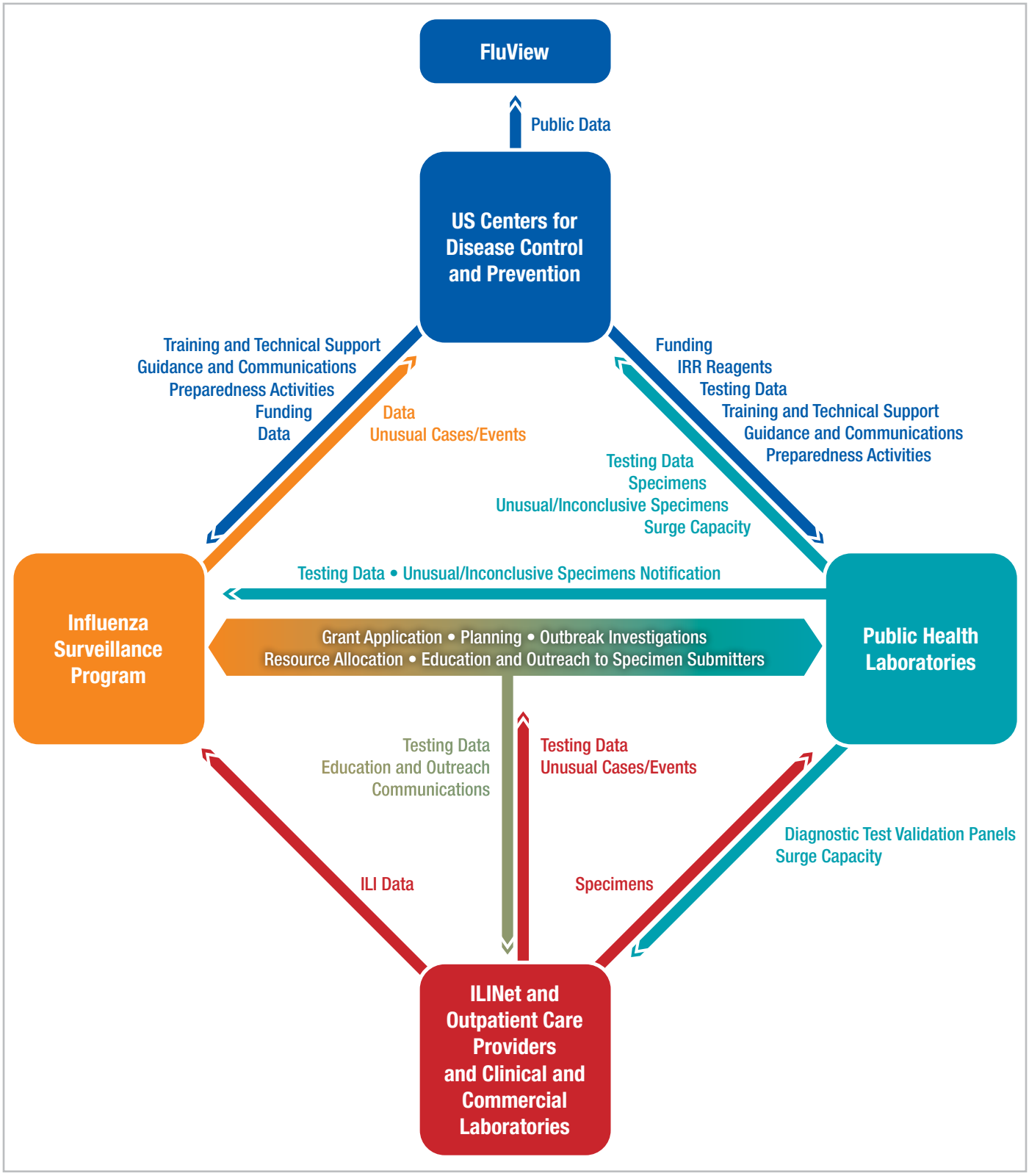


Figure 5. Essential Influenza Virologic Surveillance Partnerships and Communication. Effective virologic surveillance requires collaboration, communication and coordination between various partners.

coordinators based in state, local, and territorial health departments. Monthly conference calls and annual meetings allow for discussions about influenza virus circulation and potential new 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 and throughout each season and working collaboratively toward common surveillance goals.

Additionally, professional organizations such as APHL and CSTE provide programmatic and technical support to member health departments and facilitate communications among CDC, PHLs and epidemiologists. In collaboration with CDC, APHL sponsors three NIRCs at state public health laboratories which support CDC and PHLs and are essential to the functioning and efficiency of the national surveillance. All state PHLs submit influenza-positive specimens to NIRCs for national virologic surveillance. NIRCs act as extensions of CDC performing genomic sequencing and propagating influenza viruses to sufficient quantities for further characterization in support of national vaccine virus selection efforts and antiviral susceptibility monitoring.

Improvements to influenza surveillance can be made by leveraging existing partnerships and communication networks for influenza surveillance, clinical laboratory data, LRN and other laboratory-based surveillance activities. Strong partnerships and communication between PHLs, clinical laboratories and other influenza testing sites are important to obtain quality and consistent data and specimens. Additional examples related to key partnerships, provided through stakeholder input and pilot site activities, are described below.

PHL-Epidemiology/Influenza Coordinator Partnerships

- Conduct regular in-person lab-epi meetings to establish seasonal virologic surveillance strategies, determine appropriate sample sizes, allocate funds, and regularly assess the effectiveness of the surveillance system.
- Collaborate on grant writing, monitoring and evaluation, and outbreak response coordination.
- Establish consensus protocols for sharing influenza testing data. Examples include releasing laboratory data to a secure portal that epidemiologists can access or providing epidemiologists access to selected views in the laboratory databases.

PHL-Epidemiology-Clinician/Academic Partnerships

- Provide strategic communication from state epidemiologists and PHLs to clinicians and clinical laboratories to increase awareness of routine and enhanced surveillance or changes in clinical recommendations.
- Provide education programs to clinicians (e.g., webinars, seminars). Educational programs are often welcomed and can provide an opportunity to educate clinicians and allied healthcare professionals about influenza disease, influenza surveillance or rapid point of care tests. Trainings may provide information on specimen collection, handling and transport and may be achieved through on-site presentations, teleconferences, mailings or via online training courses.
- Collaborate with clinicians and academic researchers on studies to increase understanding

Educational Opportunities Through Joint Commission

The Joint Commission offers a free, four course series on its website. This training provides information regarding the appropriate use of rapid influenza diagnostic tests (RIDTS) for the diagnosis and treatment of influenza in the ambulatory setting. The module contains videos that demonstrate proper techniques for collecting respiratory specimens, as well as a review of information pertinent to performing point of care testing in the ambulatory setting.

Value of PHL, Epidemiology and Clinician Partnerships

Strong relationships between the PHL, state epidemiology and clinical partners are crucial to ensure consistent quality data and specimens for influenza virologic surveillance. Establishing a fruitful network of clinical partners requires dedicated resources to provide incentives, feedback and guidance. When dedicated staff routinely work with submitting clinicians on appropriate reporting, specimen collection and submission guidelines, specimens are more likely to be of higher quality and contribute to Right Size goals. Rewarding participating providers with timely results and incentives, such as RIDT kits or additional testing on influenza negative samples, reinforces the importance of their contributions.

Source: Unpublished communications with Influenza Incidence Surveillance Project (IISP) participants

PHL-Clinical Setting-Influenza Surveillance Coordinator Partnerships

- Access clinical diagnostic results to supplement influenza surveillance (see Data Management Implementation Guidance section). Commercial, web-based survey instruments are available at little to no cost (e.g., SurveyMonkey™, SurveyGizmo) to collect testing data from partners. Some tools can provide participants with an identifying login and be automatically filled with participant information to increase participation rates. Data collected can include information on a variety of agents and test methods and can be downloaded to a spreadsheet for analysis. Since a number of clinical laboratories perform their influenza testing as part of a respiratory virus molecular panel, access to these data allows for a more complete picture of circulating respiratory pathogens
- Use established networks with specimen providers to ensure and/or improve the quality and consistency of specimen submissions (see Sampling Requirements Intent and Implementation Guidance sections). For example, contact databases that already exist for LRN or courier systems for newborn screening may be leveraged to improve access to influenza surveillance specimens
- In addition to the standard communication methods, some states distribute a handbook containing instructions, forms and summary data of laboratory surveillance needs in their jurisdiction
- Promote the value of surveillance system participation and provide incentives when permissible. Incentives do not need to be monetary—they can be test results, test kits, training, certificates of appreciation, discounted registration for state conferences and reference books. A critical, intangible incentive is the added value of improved surveillance data that can be used to improve clinical management recommendations
- Provide specimen collection and shipping supplies and/or courier service to virologic surveillance participants. Most healthcare providers and clinical laboratories will not be able to absorb the cost of surveillance supplies or shipping
- Provide timely updates to specimen providers via email, web or fax. Both clinical laboratory partners and PHLs benefit from information exchange related to current influenza activity, commercial test shortages, and emerging disease threats
- Provide workshops, teleconferences, webinars, and educational materials related to influenza surveillance, proper specimen collection, and use of RIDTs
- If budget permits, provide proficiency assessment challenges, verification panels or exercises related to influenza testing and specimen packaging which may be coordinated with other state and local preparedness activities

PHL and CDC Partnerships

Collaboration between PHLs and CDC's Influenza Division is imperative for effective virologic surveillance. CDC 's Influenza Division provides vital support to PHLs and relies on data and specimens submitted by PHLs. CDC also partners with PHLs to complete the necessary validation studies for regulatory approval of new assays. Coordination between CDC and PHLs is often facilitated by APHL.

Implementation Considerations for Building Effective Partnerships and Communications

1. How does your influenza surveillance program and PHL identify the appropriate contacts among public health, healthcare providers and clinical laboratory partners within your jurisdiction?
2. How often do you routinely and collaboratively review the list of contacts to ensure that all key partners are included (e.g., identify new partners, update for staffing changes, etc.)?
3. Do you maintain a database of current contact information and influenza testing capabilities for identified laboratories within your jurisdiction?

   Some state PHLs maintain multiple separate databases—one for the LRN, one for a statewide laboratory network for surveillance, etc.—while some state PHLs have added influenza testing sites and included influenza testing capability, surveillance participation, etc., to their existing LRN database.
4. Which staff members in your influenza surveillance program and PHL are designated to coordinate outreach activities (e.g., network or surveillance coordinator/manager/advisor)? How can the lab and program work together on these activities?
5. What is your communication plan? Does it identify and link system partners?
6. How do you collaborate with other laboratories and rapid influenza testing sites to acquire virologic testing result data and specimens for further virologic testing? What could be done to improve this effort?
7. How do you collect influenza testing data from clinical laboratories/testing sites (e.g., survey tool, fax or web portal)? Is this satisfactory to you or what could be done to improve your knowledge of influenza test methods being used at clinical laboratories/testing sites in your jurisdiction?
8. How do you get information back out to providers, the public and other partners on the current status of circulating influenza types and subtypes and other respiratory viruses? For example, weekly reports on your website, a newsletter or other means.
9. How do you show appreciation and acknowledge submitter participation? Do you provide an end-of-year summary to all stakeholders about the influenza season? Do you provide individualized reports to participating laboratories and/or providers?
10. How do you relay the importance of receiving specimens for confirmatory testing, subtyping and identification of unsubtypable specimens to your clinical partners especially when the threat of a novel virus is high (e.g., H3N2v, H7N9)?
11. Does your influenza surveillance program and/or laboratory provide teleconferences, webinars or in-person training and outreach to clinician and laboratory surveillance partners/potential partners? If yes, can you use these opportunities to further build your relationships and recruit submitters? If no, why not? Do you think it could be beneficial to building partnerships and if so, how could you make it happen?
12. Is there a mechanism in place to provide feedback and corrective action to providers who incorrectly or inappropriately send specimens to the PHL (e.g., improperly shipped, incorrect form, incomplete information, sent dry swab not in media)?

QUALITY SYSTEMS REQUIREMENTS AND IMPLEMENTATION GUIDANCE

Quality Systems Requirements

Influenza programs, public health laboratories, and CDC should establish performance metrics, monitor performance on a routine basis and make improvements as needed to ensure national and jurisdictional surveillance requirements are being met in an effective and efficient manner.

In order to ensure quality virologic surveillance data, the laboratory must obtain a sufficient number of quality specimens, follow proper testing procedures and conduct data analyses. CDC and state/local jurisdictions should establish performance metrics and monitor essential components of the national influenza virologic surveillance system to ensure system quality and make improvements as needed. This section outlines key components of and considerations for a quality management system. However, each quality management system will vary, and jurisdictions should not limit themselves to this list. It is likely that existing data sources can be leveraged to assess the quality of many of these surveillance components.

PHL and Influenza Program (Jurisdictional): Quality System Responsibilities

At the state and local level, quality systems should monitor internal performance, as well as performance toward meeting national surveillance requirements, including those defined in this document. As previously noted, influenza virologic surveillance systems are complex and vary across jurisdictions, so quality systems will need to be customized for each system. The landscape of influenza testing in clinical laboratories is significantly different compared with what existed during the 2009 H1N1 pandemic and is always fluctuating. For instance, the use of molecular testing—including point-of-care devices in clinics and physician office laboratories—is increasingly common and, overall, diagnostic testing is moving closer to the patient. In general, these advancements have dramatically enhanced the sensitivity and specificity of testing in these settings.

Jurisdictions should evaluate the following elements related to influenza virologic surveillance and adjust accordingly:

- **Specimen submissions through provider networks**, ensuring consistency, quality, and quantity.
  Example: Influenza coordinator and PHL may regularly review specimen submission data for quality indicators, such as number of specimens rejected for poor quality, number of inconclusive test results, etc.
- Rapid referral of **any specimen that is unsubtypable by the CDC Flu rRT-PCR Dx Panel assay** to CDC.
- Rapid referral of samples from **patients not responding to therapy** for assessment of antiviral resistance.
- **Compliance with ELC, PHEP and other cooperative agreement and grant benchmarks** for all epidemiology and laboratory components of the surveillance system.
  - Example: Leadership should meet regularly to review grant line items, identify issues and document progress. LIMS and tracking spreadsheets can be used to document and verify deliverables are being met.
  - Example: Influenza coordinator and PHL may regularly review number of specimens received compared to number designated by Right Size sample size goals (Appendix A). Sampling may be adjusted as appropriate.
- **Timely electronic specimen-level data transmission** from PHLs to CDC. PHLIP is the preferred method of reporting.
  Example: Percentage of influenza test results received by CDC from the PHL within two weeks of the test date.
- **Capability to provide year-round molecular testing** for the detection, typing and subtyping of seasonal influenza viruses and detection of novel influenza viruses. Proficiency in PCR methods for influenza virus detection, typing and subtyping. CDC provides a quality assessment panel to PHLs at least once per year; participation in this assessment helps improve virologic surveillance quality and also provides data that help CDC assess and address training needs.
- **Usage of IRR-provided reagents**, materials and other resources for national surveillance compared to the number of specimens tested and reported to CDC. IRR reagents are provided to PHLs to support testing for national surveillance. Prior authorization from CDC is needed if IRR-provided materials are needed to support special studies.

- Systematic submission of representative influenza positive clinical materials and/or viral isolates for **national virologic surveillance** in accordance with annual CDC specimen submission guidance.
  Example: Use LIMS and tracking spreadsheets to monitor the timeliness of influenza surveillance testing and submissions to NIRCs and/or CDC. Regularly check to ensure specimens submitted to NIRCs/CDC are representative of the influenza activity in your jurisdiction and current CDC guidelines. Verify that shipment quantities and frequencies follow CDC guidelines. CDC's results website can help with retrospective analysis of shipments.
- **Staff expertise to perform each influenza test method used at the PHL.** Every PHL should have a competency assurance policy that addresses initial training, assay update training and cross- training to ensure continuity of operations in a surge event (such as the 2009 H1N1 pandemic).
- **Staff expertise and ability to adopt influenza assay modifications, add additional testing markers or adopt assay interpretation updates.** The detection of novel or variant viruses may result in new assay components or modified interpretation guidelines and staff must be prepared to handle these changes.
- Staff monitoring of the performance of the influenza test methods by **documenting control values and evaluating trends.**
- **Maintenance of an influenza specimen repository** that can be used for assay verification and validation and competency testing as needed. PHLs should store a subset of positive and negative specimens containing a mix of influenza types and subtypes at ≤-70ºC.

Benefits of Capturing RIDT Data From Clinical Laboratories

Some influenza test manufacturers have added cloud reporting capability to their reader instruments and are making available aggregated clinical testing data from clinical labs to public health officials. Data typically can be accessed through a web portal. There are many benefits to accessing these data including:

- **Timelier monitoring of influenza activity.**
  Data may be available daily in near real-time which can aid in monitoring for the beginning of influenza activity or identifying outbreaks.
- **Monitor out-of-season-positives in near real-time.**
  Since testing data may be available every day, a review can identify out of season positives as they occur. Routinely monitoring this during the summer months allows you to follow-up with clinical labs to send their positives for subtyping or genotyping which can aid in identifying novel influenza viruses.
- **Identify problems with RIDT performance.**
  Public health labs can follow-up with clinical labs reporting unusual activity such as influenza B positives being reported when statewide activity is low.

CDC: Quality System Responsibilities

CDC has unique responsibilities to look across the entire system and ensure a quality national surveillance system by conducting the following activities:

- **Cross-reference PHL influenza testing data** reported to CDC against virologic specimen submissions to CDC and NIRCs to ensure national goals are met. Clinical laboratories primarily test for diagnostic purposes, and public health laboratories primarily test for surveillance purposes.
- **Monitor national surveillance data** for timeliness, number of specimens tested and submitted and representativeness to ensure the system can effectively inform national surveillance goals. When needed, provide targeted communications to PHLs that are not consistently complying with specimen submission expectations, or to request additional specimens as needed. Targeted communications help reduce confusion about specimen requirements and focus attention on key gaps or special needs.
- **Monitor IRR reagent ordering history** in relation to testing reported to CDC. Targeted follow-up to PHLs can be an effective method for addressing excessive reagent ordering, which may be due to oversampling or unrecognized technical problems. When technical problems are identified, CDC and the PHL should collaborate to implement appropriate solutions as needed.
- **Monitor reagent supplies and expiration dates** to ensure availability of reagents to partner laboratories

WHO Laboratory Quality Stepwise Implementation Tool

The LQSI tool[32] is a web-based tool that provides a stepwise plan to guide medical laboratories towards implementing a quality system in compliance with ISO 15189. Even if you are not seeking to achieve ISO 15189 compliance, the tool is a great resource for anyone wanting to improve the quality system in their laboratory. The activities outlined in the tool are presented both as an overview of Quality System Essentials and as a structured sequence of events for day-to-day implementation. Users of the tool may focus on only one system element at a time, if desired. The tool includes a tutorial, document templates and many other resources for anyone looking to strengthen their Quality System.

Ensuring Sample Quality

At a fundamental level, the entire virologic surveillance system is reliant on having quality data generated from quality samples. 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. Specimen submitters need to be trained in proper collection technique.

Ensure Samples are of Acceptable Quality

Influenza surveillance coordinators and PHLs should provide instructions and training to specimen submitters to ensure that respiratory specimens are of high quality and are properly collected, stored, and transported.

- **Specimen Collection**

  Diagnostic test results are only as good as the quality of the specimen obtained for testing. Specimen quality depends on proper collection technique, the amount of virus present at the source, and specimen handling after collection. The amount of influenza virus shed in the upper respiratory tract declines over the course of the illness; therefore, collecting specimens as close to symptom onset as possible is recommended. Optimally, specimens for virologic surveillance should be collected within 24-72 hours of symptom onset and no later than five days post-onset of symptoms. The most appropriate specimen to collect depends upon the diagnostic test employed. This information will be provided by the test or reagent manufacturer and the laboratory performing the test.

  Specimen providers need to be trained in proper collection technique. It is ultimately the responsibility of the laboratory to ensure that specimens are properly collected. Descriptions of proper methods for specimen collection can be found in clinical textbooks, in product inserts and online however, the most effective method for learning proper specimen collection technique is demonstration by someone skilled in the collection technique, followed by practice under observation.

Specimen volumes need to be sufficient for public health laboratories to perform additional testing to further characterize the virus. In general, 3mL viral transport media collections are sufficient for screening and downstream surveillance activities. Specimens submitted with less than 3mL may not have sufficient volume for downstream sequencing, antiviral resistance testing, culturing, and hemagglutination characterization.

- **Specimen Handling**
  Specimen quality also depends on proper handling of the specimen after collection. The laboratory, in coordination with the influenza surveillance coordinator, is responsible for providing information on proper specimen handling to specimen providers.

  Specimens should be placed immediately into an acceptable viral transport medium in accordance with standard testing protocols or kit manufacturer recommendations and testing should be performed as soon as possible. Specimens may be held at 2-8°C for up to 72 hours. If a delay of more than 72 hours until specimens are tested is anticipated, specimens can be frozen at -70°C. However, multiple freezing and thawing of specimens can adversely affect the test result and should be avoided whenever possible. Virus isolates and nucleic acid extracts also require special handling.[6]

Establish and Support Specimen Transport Systems

Specimen transport is another critical component of influenza virologic surveillance. Specimen integrity must be maintained during transit. An effective and efficient process for specimen submission must account for the reliable and timely transport of specimens from clinical sites (providers) and clinical laboratories to the PHL and from the PHL to CDC or NIRCs. Specimen transport must comply with US Department of Transportation and International Air Transport Association (IATA) regulations to ensure that specimens and infectious materials are properly packaged and safely shipped.[33] Timely and efficient transport of specimens is often costly and must be adequately funded by the public health system for effective surveillance. Specimen collection and regulation-compliant transport supplies, as well as courier/carrier costs, need to be covered. Providers and clinical laboratories should not be expected to assume these costs for routine surveillance testing.

In-state commercial couriers, healthcare system couriers, PHL-provided couriers or national carriers can be employed to transport specimens to the PHL. Redundancy in transport options is important to cover disruption of any particular method of transport and to provide maximum daily service. An interstate carrier is most often used for transport to CDC or NIRCs. As of publication, CDC covers the expense of specimen shipments for surveillance purposes from PHLs to CDC and NIRCs. Information on how to use the CDC covered shipping accounts can be obtained from fluquestions@aphl.org.

In special circumstances, direct shipment from the healthcare provider or clinical laboratory to CDC may be warranted. This should be facilitated by the PHL to ensure proper handling and state epidemiologist engagement if case investigation is needed.

SURGE CAPACITY FOR INFLUENZA SURVEILLANCE, NOVEL EVENT INVESTIGATION AND OUTBREAK EVENTS

Surge Capacity Requirements

Influenza programs, public health laboratories and CDC should:

1. Maintain a year-round virologic surveillance system that is flexible and scalable for rapid, effective response to support diagnostic needs in novel influenza virus investigations and enhanced surveillance for outbreak and pandemic scenarios. The system should also have criteria to determine when to scale up and ramp down the response.
2. Ensure that PHL representatives are included in state and federal preparedness and pandemic planning activities. Address the role and resource needs of the PHL in state/jurisdictional pandemic plans.
3. Identify key partners and preparedness activities, including validation of new testing methodologies, biosafety, regulatory requirements, training, information dissemination, specimen collection and transport guidance.
4. Develop and maintain a laboratory pandemic surge plan that is integrated into a laboratory-wide COOP.
5. Establish mechanisms to determine and implement a sampling strategy for investigation following detection of a novel influenza virus. Consider the potential scenarios that may define sampling approaches, such as the need to identify additional cases and detect person- to-person transmission. Consider targeted surveillance options including clinical severity criteria, exposure risk, number of hospitalized cases/deaths and other event specific needs.
6. Establish criteria for specimen triage and decision points for performing diagnostic testing and/or expanding virologic surveillance testing. Draft scenario specific scale up and ramp down criteria that can be quickly applied when a novel influenza virus is detected, or an outbreak occurs.
7. Define laboratory testing algorithms and trigger points that may be implemented to accommodate the influx of surveillance and diagnostic specimens.
8. Periodically assess laboratory contingency and crisis surge capacity.
9. Identify and address expectations to support diagnostic testing needs, including potential support to assist clinical laboratories validate tests for the new virus.

Defining Surge Capacity in the Context of Influenza Surveillance

A strong virologic surveillance system is vital to support the detection of novel influenza viruses, outbreak investigations and pandemic response. Prior to and during an event, communication and coordination between epidemiology and laboratory leadership is essential to develop, refine, and update the strategy for virologic surge sampling and testing. While seasonal surveillance provides the expertise and infrastructure necessary for surge capacity, the response needed for a local outbreak investigation, emergence of a novel influenza virus, or a pandemic response are qualitatively and quantitatively different. As such, the term “surge capacity” can be interpreted differently across entities and settings, therefore potentially resulting in unrealistic expectations of the virologic surveillance system.

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.[34] These medical surge definitions are adapted here to provide standardized terminology to help improve planning and response:

1. Conventional Capacity

Routine virologic surveillance capacity to test an adequate number of samples to produce meaningful data with reasonable confidence levels.

2. **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 severe influenza season (e.g., increased hospitalizations, rapid transmission within the community, or a drifted virus), a local outbreak investigation or a rare/novel influenza virus investigation. Efficient use of contingency capacity may require emphasis on targeted testing based on event specific criteria.

3. **Crisis Capacity**
   A fundamental, systematic change to 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 complete all the tasks required for specimen accessioning, processing, testing and data management and analysis. Therefore, each jurisdiction may have different thresholds that will cause a shift from one stage to another.

Novel Virus and Outbreak Investigations: Epidemiology-Laboratory Collaboration

Following identification of a potential outbreak of novel influenza viruses, populations that will be targeted for testing will be determined based on:

1. **Epidemiologic Criteria**
   E.g., exposure, geographic location, travel history, or other event specific risk factors

2. **Clinical Criteria**
   E.g., severe or fatal illness

3. **Specimen Sources**
   E.g., ILINet or other outpatient healthcare providers participating in routine surveillance activities, clinical laboratories using high performing assays

COVID-19: An Unprecedented Pandemic

The public health laboratory response to the COVID-19 pandemic was all encompassing. Virology laboratories were under enormous internal and external pressures like never before seen. The political pressures of the COVID-19 pandemic necessitated PHLs to function outside of the scope of typical outbreak response activities. Right Size sample calculators were leveraged for SARS-CoV-2 sequencing; however, a comprehensive Right Size approach was not deployed during the first two years of the pandemic. Future editions of the Right Size Roadmap may further explore the utility of applying Right Size strategies for other respiratory pathogens.

Although epidemiologists should serve as gatekeepers 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. Communication and coordination between epidemiology and laboratory leadership will be essential to develop, refine and update strategies for virologic surge sampling and testing. The APHL Infectious Disease Planning and Response Framework[35] is another useful tool for planning.

Laboratories should develop and maintain a laboratory pandemic surge plan that is integrated into a laboratory-wide COOP. The surge plan should address:

- Communication/coordination with epidemiologists for specimen triage,
- Algorithm changes to improve efficiency and throughput or to meet specific surveillance needs,
- Resources (e.g., staff, cross-training, equipment, space, reagents, and consumable supplies),
- Biosafety considerations for working with novel viruses,
- Options to mitigate likely capacity gaps and bottlenecks.[36]

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

If a highly transmissible, novel virus emerges, 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 during 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 PHL leadership, will need to manage the demand for diagnostic testing and prioritize testing that is representative of the relevant populations 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 jurisdictional pandemic planning activities. 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). Expectations for state and local epidemiologists to serve as gatekeepers for specimen testing demands should be coordinated in advance and defined in the plan.

The virologic surveillance system should be flexible and scalable for rapid, effective response to support initial diagnostic needs and case identification in novel influenza virus outbreak investigations and enhanced surveillance in outbreak and pandemic scenarios. Right Size sample size calculations can be used to assess the statistical significance of the data and to provide analysis justification to other partners, including epidemiologists, public health leadership, and government entities as well as used as a justification to limit testing. This ensures that data are not misinterpreted and may also assist in obtaining necessary additional resources to gather more robust and reliable data.

PHL Surge Capacity Responsibilities and Considerations During an Event

- **CDC should use investigation mode calculators** and inform PHLs and programs if sample sizes need to be adjusted based on the situation.
- PHLs and Influenza Programs should recognize and have **a plan for managing expectations for surveillance data.** Sustaining testing to provide daily case counts will not be possible and states should consider using the Right Size sample size calculations as justification to limit testing. At some point, additional specimens will not give you any additional statistical confidence in your data to answer key surveillance questions.
- **Develop, refine and update state/local and/or CDC guidance** based on the latest information as needed for the specific event:
  - Surveillance/investigation objectives,
  - Targeted sampling approaches,
  - Initial virus detection reporting criteria (laboratory to epidemiology)
  - Ramp up/ramp down criteria.
- **Revise testing algorithms** to improve efficiency and throughput or meet specific surveillance needs.
- PHLs should **communicate closely** with health department leadership and participate in state health department emergency operations.
- **Provide timely specimen collection, testing and biosafety** guidance to clinical laboratories and clinicians.

Detailed guidance on pandemic response is beyond the scope of this document. During a large-scale event, CDC, CSTE, and APHL will coordinate to provide timely direction and support. It is important that information disseminated by CDC, state health officials and APHL to PHL directors is circulated to the laboratory staff. Management and technical staff should participate in CDC/ APHL conference calls to obtain pertinent recommendations. See CDC's Pandemic Planning Information for additional details and resources.[37]

FINANCIAL RESOURCES

Financial Resources Requirements

Influenza programs and PHLs should:

1. Coordinate planning and allocation of available funds to program and laboratory elements (staff, information technology, supplies and equipment maintenance).
2. Have effective cost accounting practices to justify resource needs and efficiently allocate available funds.

CDC, at the national level, should:

3. Coordinate distribution of available federal funds to states across multiple programs (e.g., ELC and PHEP) to minimize unintentional gaps and ensure federal priorities are supported and sustainable.

Critical Financial Resources for Maintaining an Effective Influenza Virologic Surveillance System

An optimal influenza surveillance system requires adequate resources to support all essential elements defined in this Roadmap. 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 influenza surveillance. Accurate assessments of the cost of virologic surveillance activities are critical to justify and prioritize funding.

Federal funding has continued to enhance and sustain capacity to support virologic surveillance. The US influenza surveillance system has strengthened over the past decade, particularly from supplemental funding during and after the 2009 H1N1 pandemic response. Collaborative planning and grant partnerships for funding allocations between influenza surveillance programs and PHLs is essential to ensure all parties have vested interests in participating in and contributing to influenza surveillance at levels necessary to meet Right Size targets for virologic surveillance.

Surveillance is supported by several funding streams distributed at different times depending on source. Additionally, the cost of surveillance and the availability and allocation of funds for the components of virologic surveillance varies across jurisdictions. Thus, 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 due to the complexity of the system. Optimizing resources and justifying funding requests requires accurate and thorough cost accounting at the national, state, and local level.

Federal Funding Sources

- **Epidemiology and Laboratory Capacity (ELC) Cooperative Agreement:** Currently, state/local influenza virologic surveillance systems rely heavily on CDC funding resources. In particular, the ELC cooperative agreement program is the most universal and consistent federal funding source for influenza surveillance, specifically for supporting programmatic and laboratory personnel. Health departments in all 50 states, several territories and US-affiliated Pacific Islands and several large cities receive funding from CDC via the ELC cooperative agreement program to support US influenza surveillance goals. The primary goals of the influenza component of the ELC include:
    - Establishing and supporting ILINet provider networks
    - Maintaining laboratory testing and reporting capability and capacity for year-round virologic surveillance
    - Investigating novel influenza virus cases
    - Participating in the other routine activities of seasonal influenza surveillance in the United States

  CDC supports public health influenza virologic surveillance through ELC because the work of PHLs contributes to national and global disease prevention efforts. Specimens submitted to CDC and NIRCs contribute the viruses used to assess antigenic changes that impact vaccine effectiveness; these viruses are also frequently selected as seed strains for manufacturing seasonal influenza vaccines.

- **EIP:** Active population-based surveillance in ten states for laboratory confirmed influenza- related hospitalizations.
- **PHEP Cooperative Agreements:** Provides some funding for certain pandemic planning and response activities including partner and clinical laboratory outreach, purchase of laboratory equipment and supplies, support for specimen courier/ transport systems and staffing. Many of the resources sustained by PHEP and seasonal surveillance are the backbone of pandemic preparedness.
- **Other special projects:** As resources permit, CDC supports additional studies and special projects. These programs help to expand capacity for participants and provide valuable data to advance 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.

- **International Reagent Resource (IRR):** Since 2009, CDC's IRR provides rRT-PCR reagents and performance evaluation panels to qualified PHLs to help sustain rapid virus detection and subtyping capacity. These are critical resource that significantly reduce the financial burden for state/local jurisdictions and ensures the timely availability of standardized molecular testing reagents intended for virologic surveillance. IRR is able to bulk purchase, which may be more cost effective than individual state purchases. Financial support for ancillary reagents through 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—ranges from approximately $10 to $20 per specimen.
- **NIRCs:** CDC, in collaboration with APHL, has established enhanced capacity at select PHLs to provide advanced antigenic and genetic characterization testing for all states and territories on behalf of CDC. The primary function of the NIRCs is to support annual vaccine virus selection.
- **Informatics Support:** Technical assistance teams provide training, on-site assistance and follow-up consultation to assist PHLs implement PHLIP. CDC provides the financial resources through APHL to assist PHLs with implementing PHLIP.
- **Technical Support and Training:** CDC subject matter experts are readily available to PHL and program staff to address clinical, operational, and technical questions. CDC also provides diagnostic testing of unsubtypable and other specimens of clinical interest, such as those from patients not responding to antiviral treatment. CDC, in collaboration with APHL, has provided a variety of in-person technical training courses (e.g., rRTPCR, pyrosequencing) for state and local jurisdictions at little or no cost to states to ensure that the necessary expertise is readily available at PHLs. APHL and CSTE host annual Influenza Surveillance Workshops, which convene state representatives working on influenza virologic testing and surveillance in order to provide opportunities for states to network with each other and with CDC Influenza Division staff.

It is critical that CDC be adequately funded to continue supporting state and national activities to 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.

Sustainable Funding is Critical

Influenza viruses are constantly changing. They stay ahead of testing and research and ahead of funding for testing and research. The changing virus is only one side of the equation—the changing levels of funding is the other. Laboratories experience "roller-coaster" funding levels: a surge of money in response to a crisis and cuts when a crisis has passed.

"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."

—Adapted from *Lessons from a Virus*

Prioritization of Funds

As funding is always a limiting factor, every state should determine how to achieve influenza surveillance targets to meet national and state goals. States need to direct distributed federal resources (e.g., funding, reagents, etc.) to activities that support overall national priorities. State/ local capabilities beyond those recommended as essential to meet national virologic surveillance goals will require securing sustainable state or jurisdictional funding or special study grants. When optimizing services and justifying budget requests, PHLs and surveillance programs should work cooperatively to address:

- Essential elements defined in this roadmap for national surveillance.
- Options for shared services among PHLs.
- Scalability of the surveillance system based on available resources.
- Jurisdiction-specific influenza surveillance expectations or operational issues.

Cost Accounting

Optimizing resources and justifying funding requests require robust cost accounting at the national, state and local level. There are many advantages to effective cost accounting including, but not limited to:

- Identifying the true cost of virologic surveillance.
- Planning and allocating resources for each influenza season.
- Justifying surveillance program and laboratory testing budgets.
- Assessing which surveillance components are covered by various funding sources (e.g., federal vs state funds).
- Calculating the cost that the PHL absorbs beyond the actual state or federal funds provided.
- Ensuring PHLs and programs are good stewards of existing resources.
- Determining and justifying the most efficient testing algorithm for various scenarios.
- Writing grant proposals.
- Characterizing impacts of funding reductions.

The cost of performing influenza surveillance testing varies across jurisdictions. While there is no standard method that can be applied across all jurisdictions to assess costs, at a minimum a cost analysis should include four areas related to influenza surveillance: labor, consumable materials, equipment and overhead/miscellaneous. At a high level, expenses related to each of these areas include:

- **Labor:** Laboratory, epidemiology/influenza coordinator and information technology staff salaries as well as fringe/ benefits costs
- **Consumable Materials:** Material costs for specimen collection materials (if provided to the specimen submitters by the surveillance program or laboratory), submitter incentives (if provided), reagents and testing kits used for extraction and rRT-PCR processes as well as consumables both directly and indirectly associated with PCR testing

  Note: If the laboratory is performing any additional tests as defined in the Laboratory Testing Requirements Intent and Implementation Guidance sections, costs per test should be determined for these consumables as well.

- **Equipment:** Instrument procurement, service/maintenance and depreciation costs for all equipment used for influenza testing
- **Overhead & Miscellaneous:** Facilities, surcharges, utilities, transportation of specimens to and from the laboratory, maintaining sentinel provider networks (e.g., provider communication tools), information technology support, training and travel

Implementation Questions for Consideration

These questions address suggested processes for cost analysis and coordination needed to optimize funding allocation among those involved in influenza surveillance within the state.

1. Do you have a routine meeting or other process for all involved parties to discuss grant development, planning, fund allocation and deliverable/benchmark monitoring? Who are the relevant people to be invited to these meetings? How often do/should you meet?
2. How do you determine how much it costs your jurisdiction to perform influenza virologic surveillance?
   Example: Perform a detailed cost analysis for both surveillance program and laboratory components. See the cost accounting sub-section above for some helpful tips.
3. What is your method or process for equitably allocating funds across program and laboratory elements?
   Example: Appropriate representatives of the laboratory and surveillance program meet at the beginning of each season and periodically throughout season to discuss allocation of funds and monitor expenditures throughout the season.
4. When necessary, what is your method or process to collaboratively address funding and resource reductions across laboratory and program components?
5. How are ELC, PHEP and quality management benchmarks considered in prioritization of funding allocation?
6. Has your laboratory and health department leadership met with state lawmakers to explain the importance of state support for influenza surveillance? The following references from CDC and APHL may be used and/or adapted to help with conversations with policy makers:
   - **APHL Influenza Testing Funding Fact Sheet**
     www.aphl.org/aboutAPHL/publications/Documents/ID-2018Oct-Flu-Funding-FactSheet.pdf
   - **APHL Flu Without Labs Infographic**
     www.aphl.org/aboutAPHL/publications/Documents/ID-2018Nov-Flu-Without-Labs.pdf
   - **APHL Infectious Disease Fact Sheet**
     www.aphl.org/aboutAPHL/publications/Documents/POL-2019May-ID.pdf
   - **CDC State Funding Support Fact Sheets**
     immunizationinvestments.cdc.gov/Investments

APPENDIX A: SAMPLE SIZE GOALS BY OBJECTIVE AND STATES

Novel Virus Detection Sample Size Goals

In order for the United States to meet national novel virus detection goals, each state and territory listed below must test and report the number of influenza positive specimens per week using the CDC Flu rRT-PCR Dx Panel listed in **Table 1**. Jurisdictional goals are set by dividing the total national goal among all jurisdictions by population level.

- **High Season (Peak; 1/700):** This threshold requires PHLs to test 2,095 influenza positives per week nationally using the CDC Flu rRT-PCR Dx Panel. As a general guideline, each jurisdiction should meet or exceed their 1/700 goal at least four weeks per season around the peak of the season. In seasons with higher levels of activity, meeting or exceeding the 1/700 goal for more than four weeks is likely and desirable. The four-week threshold is intended to be a minimum goal.

  Laboratories in all jurisdictions should be brought up to a minimum testing level to ensure adequate sensitivity with geographical representativeness at the peak of season. Jurisdictions with multiple laboratories (e.g., local laboratories) performing the CDC Flu rRT-PCR Dx Panel are able to include data on specimens tested at all of these laboratories to reach their goal as long as subtyping is performed. While some jurisdictions already meet or exceed their 1/700 goal for four or more weeks each season, some jurisdictions are not yet able to achieve these testing levels for various reasons, including:

  - Difficulties in soliciting screened specimens from clinical laboratories
  - Jurisdictions with large populations have high goals that are difficult to attain
  - Personnel time or other resources that may limit testing levels.

- **Shoulders (Acceleration/Deceleration Phase, 1/200):** This threshold requires testing of 598 influenza positives per week nationally. If sufficient influenza viruses are circulating, jurisdictions should aim to meet the 1/200 goal each week of the influenza season.
- **Summer/Off-season (1/4):** This threshold requires testing of 11 influenza positives per week nationally. Due to rounding and the need for geographic representativeness, our sample size goals exceed the threshold minimum. A laboratory should aim to meet the 1/4 goal every week throughout the entire calendar year (52 weeks), as long as there are influenza-positive specimens being reported from clinical laboratories.

Vaccine Virus Selection and Antiviral Resistance Sample Size Goals

To meet both vaccine strain selection and antiviral resistance sample size goals, jurisdictions need to follow annual specimen submission guidance distributed by CDC and APHL. Additionally, CDC may solicit additional specimens beyond routine guidance to help meet national goals based on availability of specific virus types/subtypes/lineages. Cooperation with these requests is greatly appreciated and helps ensure that goals are met.

This objective is achieved with influenza positive specimens submitted to CDC and NIRCs by PHLs that are broadly representative of viruses circulating within a jurisdiction based on:

- **Top priority:** Timeliness – the most recently collected viruses.
- Geography – representative of the entire jurisdiction.
- Age – includes viruses from all affected age groups
- Disease severity – representative of the range of medically attended disease severity from outpatients to fatal cases.

Situational Awareness Sample Size Goals

Situational awareness, in the context of this document, refers to determining the true percent positivity of influenza viruses among medically attended visits for respiratory illnesses. To determine percent positivity, jurisdictions need weekly testing data on 137 unscreened specimens at the start and end of the season and 325 at the peak of season in order to be 95% confident in the percent positivity with a 5% margin of error. Clinical laboratory data should be sufficient to inform percent positivity, but unscreened respiratory specimens submitted to PHLs can also be used to meet these goals.

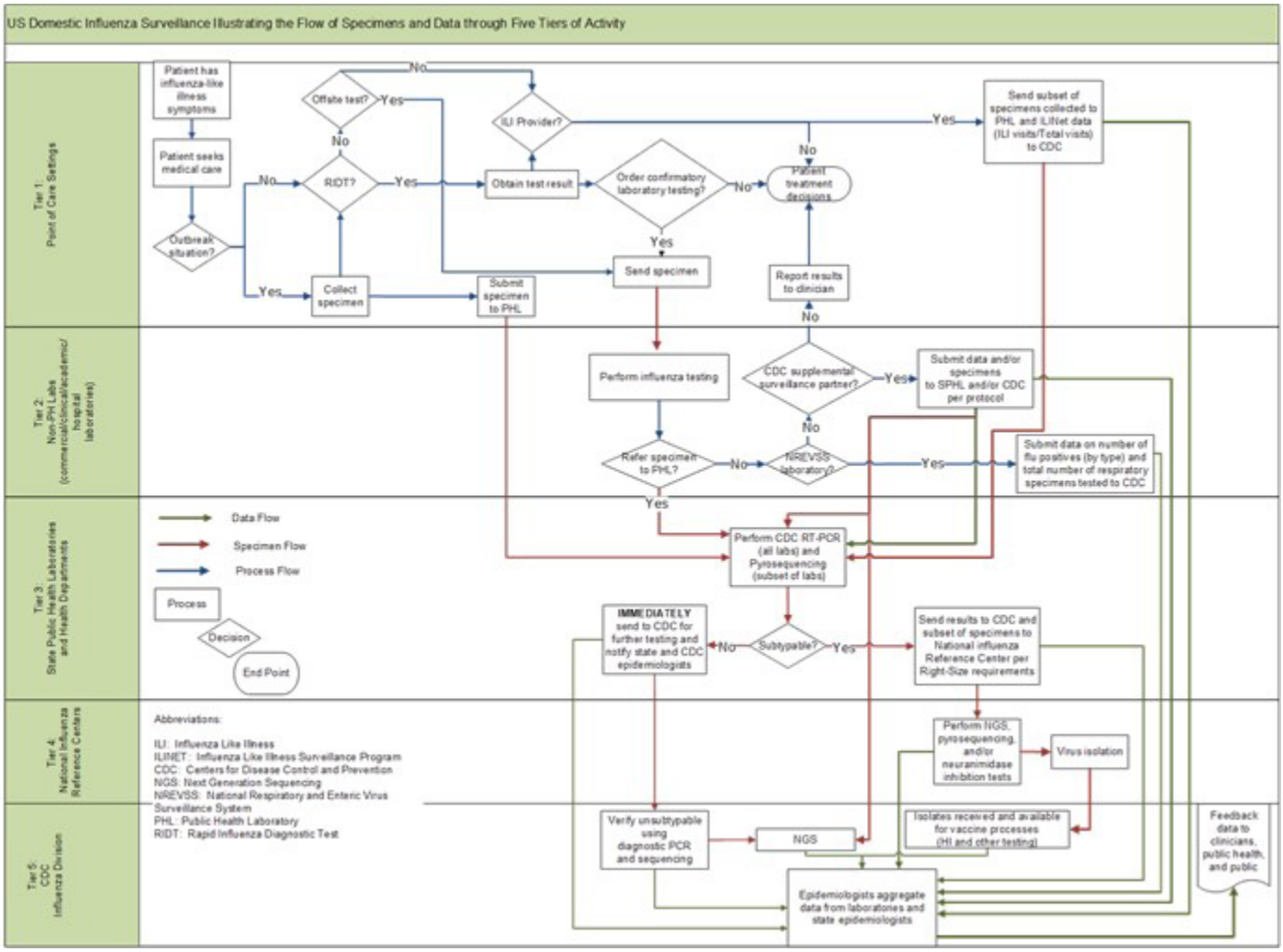
Table 1. Novel Virus Detection Sample Size Goals by Jurisdiction using 2020 United States Census populations.

State		# Influenza Positives to Test Per Week		
Name	Abbreviation	High Season Peak, 1/700 Goal to achieve ≥ 4 weeks per season	Shoulders Acceleration/deceleration phase, 1/200 Goal to achieve during MMWR weeks 40-20	Summer/Off-season 1/4 Goal to achieve: year-round
Alabama	AL	39	9	1
Alaska	AK	5	2	1
Arizona	AZ	46	13	1
Arkansas	AR	20	6	1
California	CA	251	72	2
Colorado	CO	37	11	1
Connecticut	CT	23	7	1
Delaware	DE	7	2	1
District of Columbia	DC	5	2	1
Florida	FL	135	39	1
Georgia	GA	67	20	1
Guam	GU	2	1	1
Hawaii	HI	10	3	1
Idaho	ID	12	4	1
Illinois	IL	81	24	1
Indiana	IN	43	13	1
Iowa	IA	20	6	1
Kansas	KS	19	6	1
Kentucky	KY	29	9	1
Louisiana	LA	30	9	1
Maine	ME	9	3	1
Maryland	MD	39	11	1
Massachusetts	MA	44	13	1
Michigan	MI	64	19	1
Minnesota	MN	36	11	1
Mississippi	MS	19	6	1
Missouri	MO	39	12	1
Montana	MT	7	2	1
Nebraska	NE	13	4	1
Nevada	NV	20	6	1
New Hampshire	NH	9	3	1
New Jersey	NJ	57	11	1
New Mexico	NM	14	4	1
New York	NY	124	36	1
North Carolina	NC	66	19	1
North Dakota	ND	5	2	1

State		# Influenza Positives to Test Per Week		
Name	Abbreviation	High Season Peak, 1/700 Goal to achieve ≥ 4 weeks per season	Shoulders Acceleration/deceleration phase, 1/200 Goal to achieve during MMWR weeks 40-20	Summer/Off-season 1/4 Goal to achieve: year-round
Ohio	OH	75	22	1
Oklahoma	OK	25	8	1
Oregon	OR	27	8	1
Pennsylvania	PA	82	24	1
Puerto Rico	PR	21	6	1
Rhode Island	RI	7	2	1
South Carolina	SC	33	10	1
South Dakota	SD	6	2	1
Tennessee	TN	43	13	1
Texas	TX	182	52	1
US Virgin Islands	USVI	1	1	1
Utah	UT	21	6	1
Vermont	VT	4	2	1
Virgina	VA	54	16	1
Washington	WA	48	14	1
West Virginia	WV	12	4	1
Wisconsin	WI	37	11	1
Wyoming	WY	4	2	1

APPENDIX B: INFLUENZA VIROLOGIC SURVEILLANCE SAMPLING PROCESS MAP

This process map depicts the complexities of the virologic surveillance landscape and organizes it into five major testing tiers based on where testing is performed. To best understand this process map, readers are encouraged to review the full original publication for additional context.[38]



APPENDIX C: GLOSSARY OF TERMS AND ACRONYMS

The following terms and acronyms are defined here according to their usage in this document; terms may have additional meanings beyond these descriptions.

Term/ Acronym	Definition (as used in this document)
APHL	**Association of Public Health Laboratories:** the national nonprofit organization that represents governmental public health laboratories; www.aphl.org
CDC	**US Centers for Disease Control and Prevention:** Federal organization within the US Department of Health and Human Services, to protect health and promote quality of life through the prevention and control of disease, injury and disability; www.cdc.gov
CDC Flu rRT-PCR Dx Panel	**CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel:** a nucleic acid amplification assay that detects influenza A and B viruses and further characterizes influenza A subtypes A/H1, A/ H1pdm09, A/ H3 and A/H5 (Asian lineage).
CLIA '88	**Clinical Laboratory Improvement Amendments of 1988:** the Clinical Laboratory Improvement Amendments (CLIA) were passed by the US Congress in 1988 to establish quality standards for all laboratory testing to ensure the accuracy, reliability and timeliness of patient test results regardless of where the test was performed; www.cdc.gov/clia/
CSTE	**Council of State and Territorial Epidemiologists:** an organization of member states and territories representing public health epidemiologists; www.cste.org
DOT	**Department of Transportation:** US government agency with responsibilities that include regulating the transport of dangerous or hazardous materials.
Drifted Viruses	Small changes in the influenza virus that happen continually over time. Antigenic drift is a mechanism for variation in viruses that involves the accumulation of mutations within the genes that code for antibody-binding sites, which reduces or inhibits the binding of neutralizing antibodies.
EIP	**Emerging Infections Program:** a program administered by the CDC in which a network of 10 state health departments and their partners conduct specialized surveillance, prevention and control of emerging infectious diseases.
ELC	Epidemiology and Laboratory Capacity cooperative agreements (grants) provided by CDC to support infectious disease surveillance activities in states.
ELR	**Electronic Laboratory Reporting:** the electronic transmission to public health of laboratory reports which identify reportable conditions.
ELR for Meaningful Use	Activities overseen by US Centers for Medicare & Medicaid Services in support of interoperable electronic health records, including electronic laboratory reporting, which can be used to achieve measurable outcomes.
FluView	CDC weekly influenza surveillance report, provides data and analysis of current influenza activity; www.cdc.gov/flu/weekly/index.htm
HL7	**Health Level 7:** standards developed by a non-profit, ANSI- accredited organization that provide for the exchange, integration, sharing and retrieval of electronic health information; www.hl7.org/

Term/ Acronym	Definition (as used in this document)
HPAI	**Highly pathogenic avian influenza:** influenza viruses that can cause disease in chickens when they are infected but does not relate to disease-causing capabilities in other species.
IATA	**International Air Transport Association:** responsibilities include regulating the air transport of dangerous or hazardous materials; www.iata.org
ILI	**Influenza-like Illness:** defined as fever (temperature of 100°F [37.8°C] or greater) and cough and/or sore throat; used as a measure of illness that may be caused by influenza viruses.
ILINet	**US Outpatient Influenza-like Illness Surveillance Network (ILINet):** healthcare providers in all states, the District of Columbia, Puerto Rico and the US Virgin Islands who report to CDC the total number of patients seen and the number of those patients with influenza- like illness (ILI) by age group.
IRR	**International Reagent Resource:** organization established by the US CDC to provide registered users with reagents, tools and information to study and detect influenza virus; www.internationalreagentresource.org/
LIMS	**Laboratory Information Management System:** also known as a Laboratory Information System (LIS), a software system to support laboratory operations, possibly including data tracking and exchange, sample tracking and informatics.
LOINC	**Logical Observation Identifiers Names and Codes:** a universal code system to allow the exchange and aggregation of electronic health data from many independent systems; loinc.org
LRN	**Laboratory Response Network:** a national network of more than 150 local, state and federal public health, food testing, veterinary diagnostic and environmental testing laboratories to respond to public health emergencies; emergency.cdc.gov/lrn/
MDCK	**Madin-Darby Canine Kidney:** a cell culture line used primarily for culture of influenza viruses.
MMWR	**Morbidity and Mortality Weekly Report:** the weekly publication provides timely, reliable, authoritative, accurate, objective and useful public health information and recommendations; cdc.gov/mmwr
NCRID	**National Center for Immunization and Respiratory Diseases**
Neuraminidase Inhibition	Preventing the normal function of a protein present in influenza viruses (neuraminidase) that allows the virus to be released from infected cells; also a method to determine one component of the subtype of an influenza virus.
NIRC	**National Influenza Reference Centers:** PHLs performing additional characterization of influenza viruses for national surveillance goals and annual influenza vaccine strain selection.
Novel Influenza Virus	Reassortant or animal origin virus found in humans or previously unidentified antigenic virus subtype.
NREVSS	**National Respiratory and Enteric Virus Surveillance System:** a laboratory-based system managed by CDC to monitor patterns in the detection of respiratory syncytial virus (RSV), human parainfluenza viruses, adenoviruses and rotavirus; www.cdc.gov/surveillance/nrevss/
PHL	**Public health laboratory**

APPENDIX D: ADDITIONAL RESOURCES

- **APHL's Infectious Disease Planning and Response Framework Checklist**
  A checklist to be used by public health laboratory leaders and scientists that outlines the various elements public health laboratories must address with each disease outbreak or emerging threat.
  www.aphl.org/MRC/Documents/ID_2013May_Infectious-Disease-Planning-and-Response-Framework-Checklist.pdf

- **CDC's FluView and FluView Interactive**
  FluView is a static report that provides regular summary reports of influenza activity including interactive maps, viral surveillance data, antigenic characterization, antiviral resistance, novel influenza activity and many other valuable data summaries. FluView Interactive is an online application that makes more detailed influenza surveillance data available and can be queried.
  FluVIew: www.cdc.gov/flu/weekly/index.htm
  FluVIew Interactive: www.cdc.gov/flu/weekly/fluviewinteractive.htm

- **CDC Seasonal Influenza Website**
  CDC's website provides up to date information on current seasonal influenza activity as well as critical updates regarding any emerging viruses or issues.
  www.cdc.gov/flu/weekly/fluactivitysurv.htm

- **Clinical Description & Lab Diagnosis of Influenza**
  CDC's website provides guidance for clinicians on when to test, algorithms and how to interpret test results.
  www.cdc.gov/flu/professionals/diagnosis/index.htm

- **APHL's Laboratory System Improvement Program (L-SIP)**
  L-SIP advances the efficacy of state and local public health laboratory systems through engaging partners in a guided process of performance evaluation, system improvements and periodic evaluation and reassessment. Participating member laboratories receive resources and technical assistance to guide them on their way to system excellence.
  www.aphl.org/programs/QSA/performance/Pages/default.aspx

- **PHEP Cooperative Agreements (PHEP)**
  CDC's PHEP website provides valuable resources including cooperative agreement guidance, training videos and CDC's "National Standards for Public Health Preparedness Capabilities" document.
  www.cdc.gov/readiness/php/phep/

- **Rapid Influenza Diagnostic Testing**
  Guidance for Clinicians on the Use of Rapid Influenza Diagnostic Tests.
  www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm

- **WHO Interim Global Epidemiological Surveillance Standards for Influenza (2012)**
  This document proposes surveillance objectives and describes global standards for a minimal basic respiratory disease surveillance system for the monitoring of influenza.
  www.who.int/influenza/resources/documents/INFSURVMANUAL.pdf

- **WHO Global Influenza Surveillance Network's Manual for the Laboratory Diagnosis and Virological Surveillance of Influenza**
  WHO has developed this manual in order to strengthen the laboratory diagnosis and virological surveillance of influenza infection by providing standard methods for the collection, detection, isolation and characterization of viruses.
  apps.who.int/iris/bitstream/handle/10665/44518/9789241548090_eng.pdf;jsessionid=12E17C4B2712B0A1B7EFA3C3BE32479C?sequence=1

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Association of Public Health Laboratories

The Association of Public Health Laboratories (APHL) works to strengthen laboratory systems serving the public's health in the US and globally. APHL's member laboratories protect the public's health by monitoring and detecting infectious and foodborne diseases, environmental contaminants, terrorist agents, genetic disorders in newborns and other diverse health threats.

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