REQUIREMENTS INTENT

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

Sampling

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

1. Establish a system that ensures efficient collection and timely flow of high quality specimens from the patient management tier of influenza surveillance to the CDC tier throughout the year.

2. Establish a representative network of specimen submitters using ILINet providers and/or other clinical primary care sources. Also collect specimens from hospital/clinical laboratories to ensure that a subset of specimens represents hospitalized patients. Capture unsubtypable influenza positives from clinical and commercial laboratories performing PCR methods that subtype currently circulating viruses.

3. Utilize a statistical, systematic approach to collect an appropriate, adequate number of specimens for testing that will provide reliable data with acceptable confidence limits to meet surveillance objectives and recommended thresholds of detection, including timely detection of rare/novel influenza events. The sampling methodology should limit sampling bias where possible.

4. Utilize sampling approaches that ensure specimens submitted throughout the entire surveillance specimen submission and testing process are representative of:

   • Virus types and subtypes,

   • The entire year,

   • Geographic diversity of the population,

   • Age of ILI patients,

   • Disease severity,

   • Targeted populations when necessary for specific investigations.

5. Send representative clinical specimens and/or virus isolates to CDC or a CDC-designated laboratory for national surveillance purposes, including annual vaccine virus selection, based on annual CDC criteria and guidance.

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Requirement Intent

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

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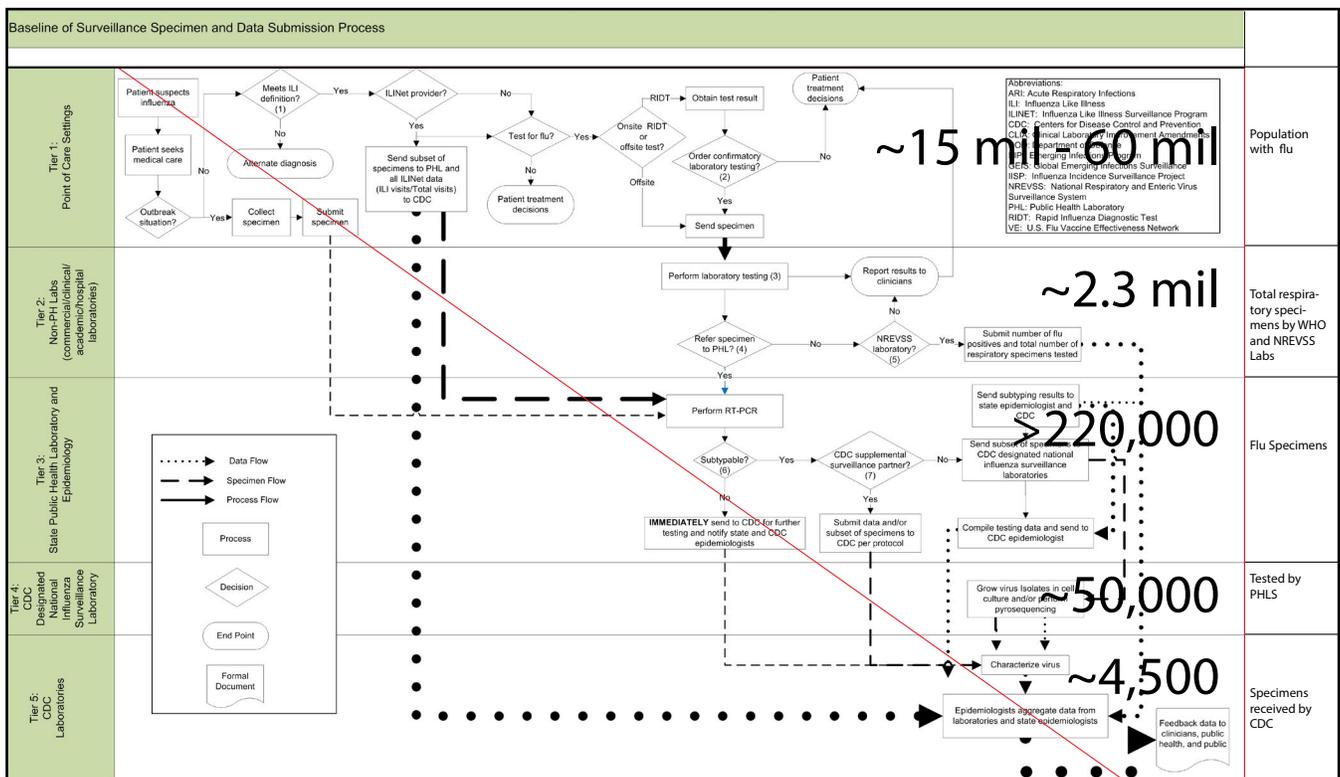

Figure 1: Surveillance Specimen and Data Submission Process. Full scale image available in Appendix A.

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

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

    a. Specimen providers and representativeness

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

- ILINet providers and other clinical primary care sources (Tier 1) who commit to regularly sending a subset of ILI patient specimens that have been sytematically selected and are not screened positive (or if screened, a random mix irrespective of test results) to state or local PHLs for testing.

- Clinical laboratories (Tier 2) who submit specimens that have tested positive and negative by PCR based on jurisdictional sampling and sample size criteria. Additionally, a subset of culture positive specimens or virus isolates from clinical laboratories that perform virus isolation should be obtained.

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

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

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

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

b. Sample Size

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

> " The calculators are one of the best tools to come out of the right size process. They are complex but helpful to answer the question: "Are we testing enough?" "
>
> —Lisa McHugh, Influenza Surveillance Coordinator, New Jersey Department of Health

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

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

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

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

c. Sample quality

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

d. Bias

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

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