OBJECTIVES: THRESHOLDS AND REPRESENTATIVENESS

In order to promote a more statistical, systematic approach to virologic surveillance, thresholds for the following key surveillance objectives have been established. 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 Interim Guidance on Use of Intervals, Triggers and Actions for Novel Influenza A (H1N1) Response.[4] The thresholds are necessary to "right size" the virologic system – this number is used in the roadmap sample size model calculators to estimate the desired number of specimens that should be tested to ensure adequate confidence in surveillance data as well as detection of novel viruses at a point where intervention can be effective. Alternately, these calculators can be used to demonstrate the level of confidence in the data obtained with the systems that a jurisdiction is capable of implementing.

Routine surveillance includes situational awareness, rare/novel influenza event detection and antiviral resistance monitoring, and provides specimens and viruses to CDC for annual vaccine virus selection. **At a minimum, the system should be sized to achieve national novel event and antiviral resistance detection thresholds and state level situational awareness needs.** Efficiency can be achieved using a sampling strategy that provides sufficient specimens to address multiple surveillance objectives when possible (e.g., the same surveillance specimens can be used to address both seasonal situational awareness and rare/novel influenzaevent detection objectives). The surveillance program should also have the capability to establish targeted surveillance of specific populations if needed.

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1. Situational Awareness for Seasonal Influenza: Virologic surveillance provides confirmation of when and where influenza viruses are circulating to inform clinical decision making and public health interventions.

    a. <u>Surveillance Objective</u>: determine the beginning and end of the influenza season and monitor the prevalence and spread of influenza viruses throughout the year.

    b. <u>Threshold</u>: 10% prevalence of influenza positive specimens among total ILI specimens submitted to a PHL or the total national system over a two week consecutive time period.

    While there is no specific threshold for action, the CDC has traditionally established the start of influenza season at a threshold of 10% positivity, calculated based on positivity of specimens submitted to the PHLs for testing by ILINet and other specimen providers and the number of screened positive influenza specimens received at PHLs. This value roughly corresponds to the CDC ILINet national seasonal baseline where the percentage of outpatient visits for ILI reaches 2.2%.

The 10% positivity threshold has been selected for use in the right size situational awareness sample size calculation based on this historical precedent. Calculation of the sample size is made using assumptions regarding medically attended ILI (MA-ILI) based on historical data. State and local surveillance programs may use alternate criteria for declaring the start or end of the influenza season. Additionally, jurisdictions may choose to alter the percent positive used in the sample size calculator to more accurately determine the amount of testing needed throughout the season or to assess the confidence level of the data provided.

In the past, ILI specimens tested in state PHLs were largely unscreened (i.e., not tested by the provider). Today a significant portion of specimens submitted to PHLs may be screened positive for influenza by the submitter (i.e., tested positive using a commercially available influenza test) which can greatly alter the PHL positivity rate. The increased reliance on screened positive specimens and the higher sensitivity of PCR methods used more commonly in many clinical laboratories and in all state PHLs may bias the influenza prevalence calculations, impacting the assessment of the scope or severity of the influenza season. Ideally, the percent positivity should be determined using specimens that have not been screened to the greatest extent possible. If data from clinical laboratory testing are being used for situational awareness, at a minimum ensure that the data are coming from sites that are performing high quality testing, and using sensitive methods such as rRT-PCR. Future revisions to this threshold may be needed in the context of changing testing and specimen submission practices.

c. <u>Representativeness</u>: specimens submitted for routine virologic surveillance to inform community, state and national situational awareness should be broadly representative of the population as a whole (age, geography, risk groups, disease severity).

2. Rare/novel influenza Event Detection: Virologic surveillance detects the emergence of reassortant, animal origin or completely novel virus subtypes in humans. The initial detection of a novel virus is always laboratory dependent and may occur anywhere in the US The sensitivity of the system to detect a novel virus at the national level relies on all states contributing specimens and data at a reasonable level proportionate with their population.

   a. <u>Surveillance Objective</u>: Detect a novel influenza virus among influenza positive surveillance specimens tested in all states at a low enough threshold for effective intervention and control measures. This objective relates to the initial detection of a novel virus which generally occurs as part of routine surveillance. Investigation of a rare/novel influenza event after initial detection (the "deep-dive") is a separate objective and is discussed in more detail in the Sampling Requirements Intent and Implementation Guidance sections.

   b. <u>*National Threshold*</u>: Different thresholds have been established for the high season (flu positivity > 20%), and low season (influenza positivity < 20%). These thresholds represent achievable levels of detection based on review of virologic surveillance data from several recent influenza seasons.

High Season: 0.14% (1/700); one novel virus among 700 influenza virus positive specimens aggregated _at the national surveillance level_ over a defined period. A minimum threshold of 0.2% (1/500) may be used for determining the sample size in states with limited testing capacity. Application of a less sensitive threshold for detection (e.g., below 1/500) would mean that more novel viruses are circulating prior to detection and would impair disease prevention and control efforts.

Low season: 0.5% (1/200); one novel virus among 200 influenza virus positive specimens aggregated at the national surveillance level over a defined period. This approximates the prevalence at which the H1N1pdm2009 influenza virus was detected in April 2009. A minimum threshold of 0.6% (1/143) may be used for determining the sample size in states with limited testing capacity.

   c. _State or Local Threshold_: Using the same detection thresholds for identification of novel viruses at a state level (i.e., 1/700 or 1/200 among influenza positive specimens tested in the state) would require a significantly larger sample size to achieve an adequate data confidence level. The resources and capacity are generally not adequate to test the number of specimens needed to generate statistically powerful rare/novel influenza event detection data at the state/local or even regional level.

   d. Representativeness:

      i. Routine Surveillance: Rare/novel influenza event detection is a component of routine virologic surveillance, specimens should be broadly representative of the population as a whole (age, geography, risk groups, disease severity).

      ii. Enhanced/Targeted Surveillance: Detection of a novel virus may be enhanced with more targeted surveillance in specific populations or risk groups, based on the most current information of risk for novel virus emergence (e.g., returning travelers from high risk areas with ILI, swine or poultry exposure). Thresholds and sample sizes may vary from those proposed for routine surveillance depending on risk scenario.

3. Vaccine Virus Selection: Virologic surveillance at the state/local level provides specimens to CDC for antigenic and genetic characterization to determine whether the circulating strains match the seasonal vaccine strains in "real time" and to inform annual vaccine virus selection. Submission of specimens should remain consistent throughout the season.

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

   b. Thresholds for the degree of difference between circulating viruses and vaccine strains are not defined here as these criteria are more appropriately established seasonally by the WHO vaccine virus selection experts. Due to seasonal variability in subtype prevalence and the specifc data and virus needs for annual vaccine virus selection and vaccine candidate development, CDC will provide guidance on specimen submission requirements at the beginning of the season and may adjust submission requirements

throughout the season as needed. Every PHL participating in virologic surveillance are expected to submit specimens to CDC or a CDC-designated laboratory in accordance with annual guidelines.

c. Representativeness: Surveillance sampling strategies to ensure appropriate representativeness for vaccine virus selection should prioritize:

   i. Timeliness – the most recent viruses.

   ii. Type and subtype – viruses representing all circulating types and subtypes. Oversampling of less prevalent subtypes may be necessary to ensure an adequate number of viruses are available for antigenic and molecular characterization and vaccine candidate development.

   iii. Geographic – CDC should test viruses with sufficient diversity to be representative of the US at a regional level; PHLs should ensure that specimens submitted to CDC are representative of the entire state.

   iv. Disease severity –viruses representative of a range of disease severities (from outpatients to fatal cases).

   v. Age – age representativeness is not an important factor for vaccine virus selection.

4. Antiviral Resistance: Virologic surveillance testing to detect antiviral resistance is performed using molecular methods for detection of resistance markers AND phenotypic resistance testing which requires viable virus. If surge antiviral resistance testing capacity is needed, genotypic testing (i.e., pyrosequencing) would be used to meet testing demand.

   a. Surveillance Objective: Detect antiviral resistant virus(es) among influenza positive surveillance specimens tested across all states at a low enough threshold for effective intervention and control measures. Currently the majority of antiviral resistance surveillance testing at CDC is performed using the same viruses that are submitted for vaccine virus selection. Some PHLs perform pyrosequencing for molecular markers of antiviral resistance, states are expected to report these results to CDC for inclusion in national surveillance FluView reports. National "percent resistance" is determined using all sources of data.

   b. Thresholds:

      National threshold: Detect oseltamivir resistance at or below 5% (1/20) prevalence among each influenza A subtype or influenza B positive specimens tested at the national level. Calculators may also be used to assess the sample size needed at other prevalence levels.

      These recommendations or thresholds may change over time depending on resistance trends or if new viruses with resistance markers emerge. A sustained increase or an unexplained jump in number of resistant viruses in the US or globally may trigger an investigation and expanded testing. Confirmed, substantial increases in resistance

may result in changes to clinical treatment guidance depending on the overall influenza prevalence, resistant virus prevalence,and geographic/temporal spread.

If there is an increase in influenza antiviral resistance outside of the US, the right size virologic surveillance thresholds may be lowered, targeted surveillance may be implemented or additional samples may be tested to increase the confidence and decrease the error in detecting a 5% prevalence of resistant viruses.

State or local thresholds: Using the same antiviral resistance detection threshold at a regional or state/local level would require a significantly larger sample size to achieve an adequate data confidence level. Although some jurisdictions may wish to report antiviral resistance surveillance data at the local/state level to help inform local provider's clinical management decisions, the resources and capacity are generally not adequate to test the number of specimens needed to generate statistically powerful antiviral resistance testing data at the state/local or even regional level. State and local laboratories choosing to perform antiviral resistance testing are encouraged to utilize sample size models to assess statistical confidence of prevalence rates generated from PHL testing. It is strongly recommended that all PHLs performing pyrosequencing routinely report testing results to CDC in a timely manner to be incorporated into national surveillance data.

c. Representativeness:

All surveillance samples submitted to CDC or a CDC-designated laboratory for antigenic characterization are tested for antiviral resistance. Surveillance sampling strategies to ensure appropriate representativeness for monitoring antiviral resistance should prioritize:

i. Timeliness – recent specimens provide the most valuable data. Testing early and peak season specimens is especially important to monitor changes in antiviral resistance profiles. (Note: Surveillance testing is generally not sufficiently timely for individual patient treatment decisions. Individual results are not reported. CDC does provide diagnostic testing on a case-specific basis. Contact CDC, fluantiviral@cdc.gov for more information).

ii. Subtype – viruses representing all circulating subtypes should be tested. Oversampling of certain subtypes may be recommended based on seasonal criteria or emergence of resistant viruses.

iii. Geographic – viruses from all states contribute to ensure sufficient diversity to be representative of the US.

iv. Disease Severity – viruses representative of a range of disease severities (from outpatients to fatal cases).

v. Outbreaks/clusters – will be investigated to evaluate geographic spread and drug exposure.

vi. Age – age representativeness is not considered to be an important factor for this surveillance objective.