Supplement F: Laboratory Guidance

IV. CDC's Laboratory Diagnostics Plan

CDC is planning and embarking on a range of laboratory diagnostics activities that will enhance the capacity to detect a reappearance of SARS-CoV and respond to and manage outbreaks. Objectives and descriptions of these activities are as follows.

Objective 1: Expand public health access to high-quality SARS-CoV diagnostics.

Activities

- Assay deployment -- CDC has deployed the SARS-CoV RT-PCR diagnostic assay under an Investigational Device Exemption (IDE) from the Food and Drug Administration (FDA). Protocols for both the RT-PCR and the serologic assay have been approved by CDC's Institutional Review Board (IRB). RT-PCR assays were deployed through the Laboratory Response Network (LRN) to selected laboratories in nearly all states; serologic assays have been deployed to nearly all state public health laboratories.

- Proficiency testing -- To assess the availability and quality of SARS-CoV diagnostics in laboratories that received CDC's RT-PCR and antibody assays, CDC will distribute a panel of positive and negative specimens for testing (proficiency panels). The receiving laboratories will test these specimens and send their results to CDC for analysis of findings and responses to a questionnaire. These data will provide information on the laboratory's readiness to perform SARS-CoV diagnostics (see Appendix F1).

- Assessment of SARS-CoV diagnostics in non-public health laboratories -- Determining the availability and quality of SARS-CoV testing in non-public health laboratories will provide an assessment of overall laboratory diagnostic preparedness. Several clinical pathology professional organizations conduct laboratory surveys and distribute proficiency panels. CDC will assist with SARS surveys and provide proficiency panels so that the professional organizations can assess the status of SARS-CoV diagnostics in their members' laboratories.

- Confirmatory testing -- Positive RT-PCR test results should be confirmed in a reference laboratory. Confirmatory testing is particularly important in areas with a low prevalence of SARS-CoV disease, where the positive predictive value of the assay is likely to be quite low. CDC will conduct confirmatory testing during the early phases of an outbreak. Other laboratories that are proficient in SARS-CoV diagnostics will participate in confirmatory testing as outbreaks escalate. Early in an outbreak, positive serologic tests should also be confirmed; later tests conducted in a proficient laboratory do not required confirmation.

  A key factor in the value of confirmatory RT-PCR testing is specimen handling. To interpret confirmatory test results, the aliquot of the specimen submitted for testing should not have been at risk for template contamination or degradation. The approach for and interpretation of confirmatory testing must consider all potential sources and types of template contamination (e.g., whole viral genome; genome portions; PCR products). Guidelines for confirmatory testing are provided in Appendix F2.

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Objective 2: Improve the ability to detect SARS-CoV by optimizing the selection and timing of specimen collection and processing.

Most patients in the early stages of SARS-CoV disease have a low titer of virus in respiratory and other secretions and require time to mount an antibody response. In one study (in patients treated with high-dose steroids and ribavirin), nasopharyngeal (NP) aspirates were found to be PCR positive in <40% of patients during the first week of illness and in >50% of patients during the second week of illness (Peiris 2003). During the second week of illness, stool specimens were found to be PCR positive in a higher percentage of patients than were NP aspirates. Limited data suggest that serum may be the best specimen for SARS-CoV PCR diagnostics during the first few days of illness.

Activities

- Specimen collection -- CDC has developed guidance for health departments and laboratorians to maximize the efficiency and accuracy of diagnostic procedures. Clinicians and laboratorians are asked to:

  - Obtain informed consent -- A signed consent form is recommended for RT-PCR and EIA testing because neither assay has been licensed by the FDA and the RT-PCR test is being used under an FDA-approved IDE. In addition, a signed consent form is required to store specimen remainders for future investigations (see Appendix F3).

  - Collect multiple specimens -- The type and timing of specimen collection is important to maximize the probability of detecting evidence of SARS-CoV infection. Since it is not yet clear which specimen type is best for detecting viral RNA, it is important to collect different types of specimens and at multiple times during the illness. Appendix F4 provides guidance on the type and timing of specimens for SARS-CoV diagnostics.

  - Handle specimens correctly -- CDC has developed guidance for specimen collection, handling, and shipping (Appendix F4). State and local health departments can use these guidelines to educate clinicians on appropriate methods of specimen management.

- Assay sensitivity -- CDC will evaluate ways to improve assay sensitivity, such as extracting RNA from a larger volume of the specimen and including a larger amount of template RNA in the RT-PCR reaction. CDC is developing IgG and IgM assays using expressed proteins as the antigens. Preliminary data suggest that antibody assays using the SARS-CoV S protein might detect an antibody response earlier in illness.

Objective 3: Ensure that SARS-CoV specimens are handled safely and that SARS-CoV diagnostic tests are used and interpreted appropriately.

Activities

- Biosafety guidance -- The laboratory-acquired SARS-CoV infection in Singapore (Singapore Ministry of Health 2003) and presumed laboratory-acquired SARS-CoV infection in Taiwan (Department of Health, Taiwan 2003) underscore the need to handle SARS-CoV specimens and SARS-CoV-infected tissue culture material safely. CDC has developed guidelines for handling these types of specimens and materials (Appendix F5) and for implementing a surveillance program in the event of a laboratory exposure (Appendix F6). State and local health

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departments can use these guidelines to educate personnel in viral diagnostic, research, and clinical laboratories about safe specimen handling and appropriate responses to a laboratory exposure.

- Test interpretation -- Clinicians should interpret SARS-CoV test results in consultation with state or local health department officials and with consideration of data on the clinical and epidemiologic features of the illness and the type and timing of specimen collection. CDC has developed guidelines to guide state and local health department staff in their consultations with clinicians about test interpretation (Appendix F7). CDC, in cooperation with CSTE, has also developed criteria for laboratory diagnosis of SARS-CoV infection (Appendix F8).

- Data reporting and integration -- State and local health departments will collect clinical and epidemiologic data on potential cases of SARS-CoV disease and report cases to CDC through a web-based reporting system. CDC will send laboratory data back to state and local health departments daily. The clinical and epidemiologic information reported to CDC and downloaded back to the states can provide a source of patient information that can help laboratorians consider appropriate testing strategies and interpret test results. With guidance from state and local health departments, CDC will facilitate access to data as requested. In addition, results of laboratory testing on any specimens submitted to CDC will be integrated into the data provided to state and local health departments, allowing timely dissemination of this information.

- Training and education – Diagnostic assays have an important role in detecting an introduction of SARS-CoV, managing a SARS outbreak, and addressing concerns about SARS. The healthcare and public health communities should be aware of the value, limitations, and appropriate use and interpretation of SARS-CoV diagnostics. CDC will provide training and educational materials that state and local health departments can use to educate clinicians and public health workers about SARS-CoV diagnostics.

- Coordination -- Coordinated information sharing among clinicians, laboratorians, and epidemiologists is central to efficient investigation of potential cases of SARS-CoV disease. CDC will assist public health laboratories and epidemiologists in developing rapid and coordinated strategies for: 1) collecting, tracking, and testing specimens, 2) interpreting test results, 3) reporting information to clinicians, and 4) communicating results to CDC, other public health officials, and the public.

Objective 4: Ensure the availability of SARS-CoV diagnostic test kits and protocols for testing other respiratory pathogens.

Activities

- Diagnostic supplies -- The supply of SARS-CoV RT-PCR and serologic test kits is limited. To ensure the availability of a sufficient number of kits to meet routine public health needs and the anticipated high demand associated with simultaneous outbreaks, CDC is monitoring both the deployment and number of kits. After patterns of use have been determined, CDC will plan the production of new kits to ensure that the supply can meet both projected baseline needs and the accelerated use associated with a SARS outbreak.

- Tests for alternative respiratory agents -- CDC will complete the development and initial evaluation of real-time PCR assays for the most important common respiratory pathogens in the United States and make primer and probe sequences and protocols available to the LRN and other public health laboratories.

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For more information, visit www.cdc.gov/ncidod/sars or call the CDC public response hotline at (888) 246-2675 (English), (888) 246-2857 (Español), or (866) 874-2646 (TTY)