June 5, 2023

Jonathan Mermin, MD, MPH
Director of the National Center for HIV, Viral Hepatitis, STD and TB Prevention
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30329

Dear Dr. Mermin:

On behalf of the Infectious Diseases Society of America (IDSA) and its HIV Medicine Association (HIVMA), thank you for the opportunity to comment on the Laboratory Recommendations for Syphilis Testing in the United States.

IDSA represents more than 12,000 infectious diseases (ID) physicians, scientists and other public health and health care professionals engaged in prevention, diagnosis and treatment of infectious diseases, including syphilis and other sexually transmitted infections (STIs). HIVMA serves as a professional community to nearly 6,000 physicians and other health care professionals working on the front lines of the HIV epidemic in communities across the country.

IDSA & HIVMA provide the following comments to strengthen the Laboratory Recommendations for Syphilis Testing in the United States and make the document more practical and useful for those who are choosing among multiple testing methods for syphilis, establishing standard operating procedures for collecting and processing specimens, interpreting test results for laboratory reporting and treating people with STIs.

IDSA & HIVMA suggest adding an executive summary and a clearly delineated list of recommendations, including the strength and evidence-level of each recommendation, at the start of the document that can be quickly referenced by laboratorians and clinicians. Where there is not a clear recommendation, it is appropriate to include factors that should be considered when choosing among testing methods. In addition, there are statements within the text that appear to be recommendations but are not enumerated as such. These should be included in the list at the beginning of the document with a clear recommendation for or against each recommendation.

In addition, we disagree that there are not sufficient data to recommend when and where to use low-cost rapid tests. IDSA and HIVMA members have real-world data and experience to support the use of rapid point-of-care syphilis tests in certain settings. Clinical examples provide evidence of the important role rapid point-of-care syphilis tests have, particularly in outreach settings, community-based organizations, mobile vans, antenatal care, emergency rooms, urgent care and labor and delivery. **We recommend that CDC include a weak recommendation with limited evidence supporting the use of rapid point-of-care syphilis tests in certain settings in those without a history of syphilis.**

The following specific comments and suggested edits are informed by input from STI experts within IDSA and HIVMA.

- Lines 211-212: The statement “There are no commercially available nucleic acid amplification tests (NAAT) in the United States” is inaccurate. There are commercially available nucleic acid *T. pallidum* molecular detection assays at numerous CLIA-certified commercial and hospital

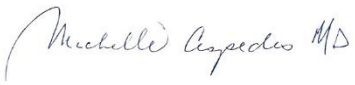
laboratories, not only through Quest. Moreover, the specific mention of Quest is unnecessary and implies endorsement of a specific commercial entity. It is correct that no *T. pallidum* PCR is FDA-cleared, but multiple CLIA-compliant laboratory developed assays are on the market.
    - In addition, line 228 states nucleic acid detection and amplification may be validated.
- Lines 223-225: Consider whether this statement should be more definitive by deleting "might." Otherwise, it may create confusion. "Several finger-stick immunoassays have been developed as rapid tests and ***might*** offer some diagnostic aid in clinical, public health, or nonclinical settings."
- Lines 223-224: "Fingerstick assays" should be described as capillary whole blood assays where the specimen is collected by skin puncture. Several rapid point-of-care assays have various FDA-cleared analytes in addition to capillary whole blood such as serum, venous whole blood and plasma. Differentiating each assay by specific specimen type would be valuable.
- Line 239-241: One large commercial laboratory may have multiple laboratory sites. We offer the following edit (in bold): Therefore, patient specimens should be tested using the same nontreponemal serologic test method, specimen type and, ideally, by the same ***laboratory site***.
- Line 256-258: We offer the following edit (in bold): "In these situations, the titer range of the automated test must be considered, and specimens ***should*** require reflex testing using a manual RPR procedure to establish an endpoint titer at either the lower or upper bounds prior to reporting.".
    - This is consistent with line 300-301: "Serum samples tested with some automated RPR serologic tests are outside the dilution range of the test should be reflex tested using a manual RPR."
- Line 362: We recommend clarifying whether rapid point-of-care anti-treponemal assays are considered manual given that none are currently automated.
- Lines 369-370: Delete this sentence as the audience for these recommendations is U.S. laboratorians and clinicians: "The manual treponemal *T. pallidum* hemagglutination assay (TPHA) and microhemagglutination assay for antibodies to *T. pallidum* (MHA-TP) tests are no longer available for in vitro diagnostics in the U.S."
- Line 381: We feel that the lack of published performance data on dried-blood spot specimens for anti-treponemal antibody testing is problematic. CDC should collect and publicize those data from laboratories.
- Line 782: We feel there is a need for interpretation of maternal versus newborn lipoidal titer levels and the implication if one is 4-fold higher or lower than the other.
- Lines 992-993: Similar to the comment for lines 211-212, we feel that a specific commercial laboratory should not be specified when multiple commercial laboratories have TP molecular testing available.
- Lines 1044-45: We recommend specifying limitations with molecular testing in CSF specimens. Some clinicians might find value in a positive test result; however, the clinical significance is unknown.
- Line 1061: We do not agree that "there is a paucity of published information related to their real-world use and test performance in the United States." This should be amended to include

recognition of multiple published peer-reviewed studies and FDA data for the Syphilis Health Check and Dual Path Platform (DPP) HIV-Syphilis assay.[1, 2]

- Lines 1111-1112: Laboratories often fail to report all the necessary and required data elements for reporting. CDC should recommend that laboratories should not test specimens without all the required data elements for reporting. Current surveillance activities are greatly compromised by the laboratory failure to report all required data elements. Public health departments, laboratory field services and the Centers for Medicare and Medicaid Services should inspect and hold laboratories accountable for incomplete reporting.

Thank you for the opportunity to provide these comments on this important document. As cases of syphilis in the U.S. continue on an upward trajectory, these recommendations provide needed guidance for diagnosis of syphilis in the U.S. Please contact Eli Briggs, IDSA director of public policy, at ebriggs@idsociety.org or Andrea Weddle, HIVMA executive director, at aweddle@hivma.org with any questions.

Sincerely,



Carlos del Rio, MD, FIDSA
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[1] Kalou MB, Castro A, Watson A, Jost H, Clay S, Tun Y, Chen C, Karem K, Nkengasong JN, Ballard R, Parekh B. Laboratory evaluation of the Chembio Dual Path Platform HIV-Syphilis Assay. Afr J Lab Med. 2016 Sep 15;5(1):433. doi: 10.4102/ajlm.v5i1.433. PMID: 28879115; PMCID: PMC5436406.

[2] Fakile, Yetunde F. PhD*; Brinson, Myra BS, MT (ASCP)†; Mobley, Victoria MD, MPH‡; Park, Ina U. MD, MS*; Gaynor, Anne M. PhD§. Performance of the Syphilis Health Check in Clinic and Laboratory-Based Settings. Sexually Transmitted Diseases 46(4):p 250-253, April 2019. | DOI: 10.1097/OLQ.0000000000000974.