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Biomedical Research Priorities for Modern Syphilis Clinical Management, Diagnosis, and Vaccines: Overview and Commentary for Unit 1

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Abstract

The first session at the 2016 Syphilis Summit provided an opportunity for laboratory researchers and clinicians to comment on gaps in biomedical knowledge and technologies. Predominant themes in the presentations and discussion included the need for optimization of existing diagnostic tests, commercial availability and FDA approval of nucleic acid amplification tests for primary and secondary syphilis, development of sensitive and specific new blood tests for diagnosis of active (vs. treated) syphilis infection, clarification of the best measures for adequacy of response to treatment, continued study of complications of syphilis including neuro- and ocular syphilis, and development of a safe and effective vaccine that will protect against transmission and complications of disseminated infection (including congenital and neurosyphilis). Renewed and sustained support of biomedical syphilis research and an influx of talent could move the needle in the fight against this re-emerging ancient disease.

Keywords

Syphilis; vaccine; neurosyphilis; diagnosis; treatment; prevention

INTRODUCTION AND OVERALL FINDINGS

In recent decades, syphilis elimination appeared within reach. Unfortunately, not only has syphilis re-emerged, but the biomedical research landscape is also left with limited human and financial resources to counter rising rates. The purpose of the first session was two-fold: first, to provide a rare opportunity to bring together remaining biomedical syphilis experts, and second, to seek their counsel for setting research priorities. These are listed below. In addition, several noteworthy themes were discussed:

- There are many open basic research questions on the natural history of syphilis. Much of our “knowledge” concerning the natural history of syphilis arises from studies conducted in the pre-antibiotic era, and these may be confounded by

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other medical conditions not recognized at the time. This includes a more in-depth definition of specific immune responses, the antigens that trigger such responses, and the level of protection induced by these responses, as defined with modern immunological approaches in both the rabbit model and in human infection. This will require development of immunological reagents for the rabbit, which is an excellent small animal model for syphilis. Research on the interaction of syphilis with co-occurring infections such as HIV should be included. Many questions remain unanswered despite the public's long awareness of the disease and despite substantial biomedical advances for more recently emergent infections such as HIV. The perception among many politicians and the public that syphilis has disappeared, and the stigma surrounding this infection, has left it the "poor stepchild" in terms of attention.

- Although research has identified potentially improved antigens for diagnostic tests, the perceived lack of a market makes many diagnostic companies reluctant to invest in development of novel, specific, and sensitive diagnostic tests and effective disease management protocols. In addition, protective vaccine development has been left wanting and the antimicrobial pipeline has been anemic with little advancement since penicillin became available in the 1940s. There is a surprisingly thin landscape of development initiatives employing modern-day technologies in these areas. Most striking is the lack of an FDA-approved nucleic acid amplification test for GUD (genital ulcer disease) to better diagnose primary syphilis.
- Few experienced biomedical researchers and clinicians remain. It is difficult to attract new talent to this field due to the difficulty in working with *Treponema pallidum* and lack of research funding to sustain their careers. For example, despite the dramatic rise in syphilis cases, the number of US basic science laboratories studying the organism or disease has remained static and low; their grant funds have been reduced compared to 10 years ago; and several experienced *T. pallidum* investigators are nearing retirement age. Given the rise in syphilis cases, young clinicians in large cities where there are STD Clinics are being given the opportunity to see cases of syphilis, but medical schools are still not including STDs, other than HIV, in their curricula in proportion to the STD problem in the US.

As a follow-up to the summit, the findings were described and disseminated to a diverse audience and diverse public health entities in the document "Syphilis Call to Action – Let's Work Together to Stem the Tide of Rising Syphilis in the United States" (1). In brief, CDC calls on partners, including biomedical scientists, to develop new tools for syphilis prevention, detection, and treatment, and to generate interest in the field. Moreover, identified priorities include the following:

1. Develop and bring to market novel syphilis tests to rapidly diagnose active (vs. treated) infection in easy-to-obtain samples (including in blood) and in all disease stages.

2. Conduct clinical research to support evidence-based recommendations for clinical management of all disease stages, including management of treatment non-serologic response, repeated infection, neuro- and ocular syphilis, and infection is persons living with HIV.

3. Promote research on effective vaccine design, acceptability, cost, and potential impact on the epidemic.

4. Invigorate training of biomedical and clinical researchers, and address basic biological research questions (e.g., genetics, immune response, pathogenesis) in order to galvanize future technological advances.

What follows is a summary of specific research priorities as identified during the structured discussion portion of Unit 1. Experts were invited to respond to five prepared questions, and to identify specific research gaps within these topic areas.

RESEARCH PRIORITIES

Structured topic 1

I.1. "How do we optimize the reverse sequence algorithm to minimize diagnostic errors or overtreatment? Is there a need for more data collection/ direct comparisons of traditional and reverse algorithms using clinically defined specimens?"

Discussion summary: The reverse testing algorithm with its prioritized treponemal test is gaining in popularity in US laboratories because it allows automation of the initial test. Because of the recognized rate of false positivity in treponemal tests, this change is increasingly leading to inaccurate case identification, especially during screening of persons in low syphilis prevalence settings. Ensuing problems can be confusion among medical providers who receive test results, anxiety and stress for the patient and their partners, and harms of potential overtreatment. In addition, there is a lack of clarity on optimal treponemal and nontreponemal test selection and interpretation, and on whether and when a second treponemal test is needed.

Identified priorities:

- To conduct careful examination of the reactive "cutoff" value, optimal serum dilution for testing, modification of the technical aspects of the existing tests to minimize false negative reactions while maintaining acceptable sensitivity.
- To explore development of new EIA/CIA tests using other *T. pallidum* antigens (beyond the 3 or 4 antigens used in all current tests).
- To evaluate the use of the reverse sequence algorithm in different scenarios and prevalence settings in comparison to the traditional algorithm, including during treatment and follow-up. Cost, the role of the epidemiologic context, and health care setting should be considerations in the design of evaluations.
- To conduct comparative evaluations of existing treponemal tests using well defined clinical specimens from patients with all stages of syphilis and

populations for whom screening is recommended. In particular, there is a need to address the value, type, and interpretation of a second treponemal test in the reverse algorithm.

- To develop evidence-based recommendations for syphilis diagnostic testing, including Rapid Testing.

Structured topic 2

I.2. What is the value of Rapid Syphilis Tests (RST) for diagnosis of syphilis in the US? Can they be used effectively to stem increases in the US and in what settings? Should we be developing another algorithm for RST use?

Discussion summary: There is currently only one FDA-approved, CLIA-waived RST in use in the US. It is a treponemal antibody test and does not include non-treponemal antibody testing. Its usefulness has not been sufficiently evaluated with regard to patient management, performance, and benefit in various settings. Evaluation data and CDC recommendations are needed to guide its use, including concerning the suitability of different biological specimens, and quality-controlled implementation. Additional POC tests, some already well-studied in international settings, should be evaluated in the US so that tests with optimal sensitivity and specificity can become available for use in the US, particularly in emergency rooms and delivery rooms where women lacking prenatal care present for delivery. This should include the dual path POC test that includes nontreponemal and treponemal antigens and POC tests that also include HIV.

Identified priorities:

- To evaluate test performance in various settings (clinical, including STD clinics, outbreak settings, field investigations, community-based organizations (CBOs), emergency departments), and compare results to laboratory-based algorithms.
- To evaluate overall outcomes of patient management, morbidity averted, and cost when RSTs are used in comparison to the use of lab-based tests.
- To foster research and development of additional treponemal antibody RSTs, non-treponemal antibody RSTs, and most importantly, new technologies that will ultimately allow rapid identification of active infection by directly detecting *T. pallidum,* especially in whole blood and CSF.

Structured topic 3

I.3. Direct detection of *T. pallidum* is a challenge in the US today. Few labs have the capability to perform darkfield microscopy. PCR detection in primary and secondary syphilis from lesion material is possible, but remains a lab-developed test. How can this assay be standardized and moved forward for FDA approval?

Discussion summary: Being able to directly detect active *T. pallidum* infection especially in genital lesions with techniques common to modern laboratories would be a game changer for syphilis diagnostics. It would likely allow more accurate and faster diagnosis of infection in the most infectious stage (i.e. primary) of syphilis. This has the potential to change patient

management by reducing misdiagnoses of primary syphilis. It could also reduce the epidemic by allowing more timely treatment of infectious syphilis, thereby preventing transmission to sexual partners. Sensitive *T. pallidum* PCR tests have been developed, but have not been cleared by FDA. Their application for differential diagnosis of GUD (HSV-1/2, *T. pallidum*, and other ulcer-causing diseases) is documented but has not been substantially implemented. This approach thus has untapped potential for stemming the tide of rising syphilis. Recent approvals of several HSV-1/2 PCR assays for genital lesion specimens may provide a new opportunity and business model for *T. pallidum* diagnostics, as HSV/*T. pallidum* multiplexed tests could be used for GUD diagnostics.

Identified priorities:

- To further develop and bring to market HSV/*T. pallidum* multiplexed PCR tests for GUD diagnosis. Additionally, *T. pallidum* PCR tests in general need to be further developed and evaluated in terms of their sensitivity and specificity on a range of specimen types, including from a variety of anatomical sites (lesions swabs, skin scrapings, blood, CSF, ocular fluid, mouth, urine, amniotic fluid, cord blood, placenta).
- POC nucleic acid amplification tests, or other direct detection tests, would be particularly useful in STD Clinic settings.
- To explore other technologies or approaches (e.g., MALDI-TOF biomarker identification) for diagnosis of active infection
- To create mechanisms for sharing of well-characterized clinical specimens (e.g., blood, serum, CSF, amniotic fluid) with associated clinical data for patients with all stages of syphilis, those living with HIV, those pregnant, and those with and without neurologic complications, as is needed for test development and validation.
- Explore development of low tech PCR tests such as LAMP (loop-mediated isothermal amplification) for use in low resource settings.

Structured topic 4

I.4. During clinical management of patients after antibiotic treatment, with potential reinfection, or during pregnancy: how well do non-treponemal titers reflect syphilis disease activity? What clinical decision should be based on changes in non-treponemal antibody titers (fluctuation, serofast, fourfold decrease)?

Discussion summary: The rate and extent of reductions in antibody titer in response to treatment in patients with and without a history of treated syphilis or increases in titer after treatment or re-infection remain insufficiently characterized and understood, yet key syphilis treatment decisions are based on them. Agreed-upon, standard definitions for rates of antibody titer declines that ideally correlate with clinical cure are needed. Moreover, the term “serofast” lacks a clear definition, and there is little consensus about when concern is warranted regarding serofast or fluctuating titers after treatment, especially in those living with HIV or in pregnancy. Therefore, more research is needed, and selected previously

conducted studies need to be repeated, using modern techniques and reagents. This should include follow-up of adult syphilis in those living with HIV, maternal syphilis, fetal syphilis, and congenital syphilis. Many studies have been uncontrolled or retrospective, and are therefore difficult to interpret.

Identified priorities:

- To conduct well-designed prospective cohort research on clinical outcomes of patients and their serological responses (both non-treponemal and treponemal), in persons with or without HIV co-infection, in females with and without pregnancy and in neonates with congenital syphilis.
- To explore new biomarkers (e.g., cytokines, T cells responses, others) and other technologies (e.g., PET scans, ultrasound [congenital syphilis]) in evaluating response to therapy and as measures of active infection.
- A careful study of IgM titers should be conducted, both in untreated persons and longitudinally following treatment, to determine whether there is a role for IgM in assessing active infection, and in determining efficacy of treatment.

Structured topic 5

I.5. How does HIV modify the natural history of syphilis infection and should this impact clinical management? If so, how?

Discussion summary: The interplay of *T. pallidum*, HIV infection, and host immune function remain insufficiently understood, as is the impact of repeated syphilis infections/ treatment and HIV antiretroviral therapy. There is a paucity of data on effectiveness of syphilis treatment in HIV-positive persons in the ART and viral suppression era. There is a lack of clarity around the potential benefits of more frequent STI screening (i.e., between recommended HIV care visits) in people living with HIV. Moreover, awareness of the adverse health outcomes of adult syphilis such as neuro-, ocular and otic syphilis has been raised in recent years, in both HIV-positive and -negative persons. Addressing the benefits of lumbar puncture to guide therapy with a goal of preventing adverse clinical outcomes, and a sensitive and specific diagnostic test for neurosyphilis are urgently needed.

Identified priorities:

- To conduct a randomized, prospective cohort study to determine the benefit of lumbar puncture at various stages of syphilis to improve clinical outcomes.
- To determine the expected rate of neurosyphilis, ocular, and otic syphilis in all stages of syphilis in the post-antibiotic era and post-ART/immune suppression era.
- To evaluate timing of syphilis treatment in persons newly diagnosed with both HIV and syphilis, particularly with regard to initiation of HIV treatment.
- To develop mathematical models of cost and benefit for frequency of STI screening in persons living with HIV.

- To conduct a longitudinal cohort study of the effect of current anti-retroviral treatment on syphilis manifestations, progression, and response to syphilis treatment, adjusting for CD4 count and level of immune reconstitution.

CONCLUSIONS AND SUMMARY

The discussion of structured topics allowed experts to discuss concrete, achievable research priorities on current issues in syphilis laboratory science and clinical management. Furthermore, it is possible to tackle unexplored areas of basic biomedical syphilis research concerning the natural history of the disease. This includes a thorough description of immune responses to *T. pallidum*. Such an investment will lay the foundation for potentially seminal discoveries that may lead to better and faster diagnostic tests, more efficacious antimicrobials, evidence-based disease management, and even a protective vaccine. These will ultimately be needed to substantially advance syphilis prevention and intervention.

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SUMMARY

The 2016 Syphilis Summit proposed renewed and sustained support of biomedical syphilis research, and recommended that an influx of talent could accelerate the fight against this re-emerging ancient disease.