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Advances in Syphilis Diagnostics to Address the 21st-Century Epidemic

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Guest: Dr. Joshua Lieberman is an Associate Professor of Laboratory Medicine and Pathology at the University of Washington in Seattle.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett.

Twenty years ago, new cases of syphilis were vanishingly rare but since that time, the rate of new infections has increased thirtyfold. Importantly, the rate of increase is highest in women, with a rise of almost 900% since 2013. This adds another dimension to this rapidly developing public health issue as increased rates of in women have led to a dramatic increase in the number of congenital syphilis cases. Complicating matters, the current syphilis epidemic can be attributed to a number of factors including social determinants of health and an inconsistent supply of penicillin.

Furthermore, laboratory testing for syphilis has remained essentially unchanged for decades. With the problem of this complexity and scale on our hands, can the clinical laboratory help? A review article, appearing in the September 2025 issue of *Clinical Chemistry*, draws attention to this public health challenge, explaining how we got here, why it's a problem that needs attention, and what clinical laboratorians can do to turn the tide. In this podcast, we are joined by the article's lead author. Dr. Joshua Lieberman is an Associate Professor of Laboratory Medicine and Pathology at the University of Washington. He is the Assistant Director of the Molecular Microbiology Laboratory and Associate Director of the pathology residency program.

Dr. Lieberman, in your review article, you and your co-authors stressed the recent growth in syphilis cases. So, to get us started here, could you tell us a little bit about where we stand in terms of disease burden?

Joshua Lieberman: Yeah, sure thing. So, in the late 1990s, syphilis was nearly eradicated in the United States. Unfortunately, success breeds complacency. And so for 20 years, we've seen a steady growth in cases. Most recently, more than 200,000 cases were reported for the calendar year 2023. That's the most recent annual data that CDC has published. These data describe the U.S. experience and really show that the number

of cases and the incidence, that is the number of new cases each year, rivals that from the 1950s. To add a little bit more context to the number, in that same 2023 year, the CDC reported 600,000 cases of gonorrhea and 350,000 positive influenza tests. So I think we can really see that the incidence of syphilis cases is up there.

We are also seeing as part of this more late-stage syphilis and more congenital syphilis than we have in decades. There were nearly 4,000 cases of congenital syphilis in 2023 alone, compared to just under 500 in 2014.

Bob Barrett: What is the impact of that increased congenital syphilis case number?

Joshua Lieberman: You know, I'll give you three examples. First, syphilis is an important cause of pregnancy loss, stillbirths, and neonatal deaths. Congenital syphilis is also associated with preterm birth, and for babies who are born with syphilis and survive, they have longer hospital stays and higher hospital costs than babies born without syphilis in hospitals. So, hospital stays increased from a median of about a day and a half to a median of 10 days, and hospital costs are about tenfold higher median hospital costs. So that's point one.

Point two is about half of congenital cases are asymptomatic, at least it first. So the disease may not manifest for days to months after birth. And then the ability of these infections, of syphilis in general, that pass under the radar is sort of a hallmark of the infection with the causative bacteria, *Treponema pallidum*, in general and it's relevant for my third point, longer-term outcomes of congenital infections.

So, those long-term outcomes can be really profound in babies. You know, of those symptomatic newborns, more than half, something like 60%, have neurological involvement such as seizures or cranial nerve deficits. They may have strokes or eye abnormalities, and some consequences may develop later or present later, such as skeletal or tooth abnormalities, hearing loss, or again later stage eye abnormalities.

Bob Barrett: Now doctor, I understand that the bacterium that causes syphilis, *Treponema pallidum*, is still sensitive to penicillin, so it seems like we should be able to treat these cases pretty easily. What are the obstacles to eradication, or stated differently, how did things get so bad?

Joshua Lieberman: It's a great question. *Treponema pallidum* is universally sensitive to penicillin, but part of the problem is that penicillin is actually hard to make. As I understand it, it's produced biologically in a bioreactor system, not through sort of conventional chemical synthesis. And so companies that

make these drugs, or make penicillin, can't really scale up production quickly or easily. And that's particularly true for the injectable forms that we need to treat syphilis. You know, as cases of syphilis has increased, that's driven demand for injectable penicillin and production can't keep pace, so we've had these recurrent drug shortages. Now, when we've had drug shortages of penicillin, we've saved doses for the highest priority use cases, particularly syphilis in pregnancy.

I'll also point out, maybe cynically, that there's not a lot of money to be made in producing penicillin. It's an old drug, it's off patent. So as with many antibiotics, this becomes a market failure with the economic incentives to make the drug simply aren't there. Now, you may be wondering if there are other drugs to treat syphilis and the answer is a pretty heavily qualified "yes." Penicillin has a huge advantage in that for uncomplicated primary syphilis, a single injected dose is curative. Our other primary antibiotic is doxycycline but unlike penicillin, treatment with doxy means twice daily dosing for two weeks. And I can speak personally, but I think anyone who is taking medications for two weeks understands how easy it is to miss a dose, and now imagine if you don't have a safe place to live, if you're struggling to put food on the table, or other social determinants of your health distracting you.

One really important take-home point that I'd like to emphasize for our listeners is that azithromycin will not work to treat syphilis. And this is important because this macrolide antibiotic used to be effective as a single dose, but now, more than 99% of cases across all demographics in the United States are resistant to azithromycin and macrolides broadly. There are other drugs that are being evaluated, but they all require multiple doses and it's harder for patient compliance. One example, ceftriaxone, actually requires daily injections for we think 10 days, but we're still figuring out what the ideal dosing strategy. One final take-home point on why eliminating syphilis cases is really hard, there is no vaccine and recurrent cases are possible, and this is because the bacterium has this really extraordinary capacity to generate diversity in its major surface protein, and thus avoid protective antibodies that are produced in response to either an infection or a vaccine.

Bob Barrett: Your review article is really about the role of diagnostic tests in addressing the syphilis epidemic. Can you briefly describe the current gold standard for syphilis testing?

Joshua Lieberman: Yeah, sure thing. So, to diagnose syphilis, we have to test for two different types of antibodies, what we call treponemal and non-treponemal antibodies. So the treponemal antibodies are what you classically think of the body producing a response to infection, IgM and IgG that recognize

the pathogen. These are positive for life and our tests don't distinguish between the two classes of antibodies. Non-treponemal antibodies are better called lipoidal antibodies. These biomarkers and we primarily rely on RPR [rapid plasma reagin] are called lipoidal because they recognize cardiolipin. That's a lipid that the bacterium scavenges from host cells and puts into its own cell wall. Since RPR concentration in serum correlates with disease activity, we can follow positive tests with quantitative RPR testing to monitor for response to treatment.

Since these treponemal antibodies tell us about any history of infection and RPR tells us about whether the patient has an active infection, we have to do both in a stepwise screening algorithm. Either test can come first but unless you know a patient has a history of syphilis, you need both. If you know there's a history of syphilis, we can jump right to quantitative RPR. The combination of the two tests also helps mitigate the risk of false negatives and false positives. And finally, I'd add that these tests are highly sensitive. We think about 85 or 90% sensitive in primary syphilis and approaching 100% sensitive in secondary disease. They're also pretty cheap and most laboratories can run them.

Bob Barrett: This all sounds pretty straightforward. Why can't these assays meet the needs of the current epidemic?

Joshua Lieberman: That's a key question. You know, I sort of hinted earlier that syphilis is just a sneaky, sneaky pathogen. Symptoms of early disease can be easily missed. Many, but not all primary lesions are painless. And if untreated, the disease then waxes and wanes. So it can look like patients, their symptoms have gone away, but then can reappear in essentially any anatomic site. So if you don't think of syphilis when you see a patient, you might not get the right testing. You know, and I think congenital syphilis is a really good example of this, or maybe a really depressing example of this. There have been a couple of publications from CDC's division of STD prevention that have identified recurrent missed opportunities to prevent congenital syphilis, and laboratory testing is important part, but not the whole story.

So the current guidelines really strongly recommend syphilis testing early in pregnancy, but a lack of timely testing or failure to document test results accounts for about a third of misdiagnoses. So what happens if you get the testing orders right? And here's where I want to highlight three major holes in our testing strategies. So, the first issue is turnaround time, turnaround time, turnaround time. For many of our patients, like those seen as outpatients in sexual health clinics or pregnant patients who are about to deliver, it's really important to make decisions right there with the patient in front of a provider.

We do have point-of-care testing for our treponemal tests. But what we really need are point-of-care tests for the lipoidal or non-treponemal antibodies like RPR. That's so we can know if the disease is active and needs treatment or if the positive treponemal test reflects past syphilis. The current treponemal point-of-care tests really aren't bad. The positive predictive value of those tests ranges from about 20 to 50% depending upon patient population. But in my view, there's a major gap in our diagnostic testing, which is that lack of a point-of-care RPR.

The second big hole I wanted to point out is that it takes about two weeks from infection for your antibody test to turn positive. So, I'd really love to see better diagnostics for early disease. There's evidence from some very good studies that molecular testing may have utility here. If you add very sensitive molecular tests to conventional antibody screening, you can increase early case detection by about 20%. Now, current molecular tests that detect nucleic acid from the bacterium are all lab-developed tests. There are non-FDA-approved tests that have been developed for central laboratory instruments. But in either format, these take time to resolve. You know, in the order of at least a couple of days depending upon batching strategies. So what I'd really like to see is a point-of-care molecular test that is sensitive enough to increase case finding and guide treatment decisions while that patient is sitting in front of a provider.

The third major gap in our testing that I wanted to highlight is diagnosing late-stage or disseminated syphilis because these are important manifestations and really morbid manifestations for patients. In our antibody tests in cerebrospinal fluid, for example, have variable sensitivity and specificity. Molecular tests can help, particularly in cellular tissues, but organism burden in CSF, or cerebral spinal fluid, and ocular fluid can be extremely low, which limits the sensitivity of molecular detection.

Bob Barrett: Well finally Dr. Lieberman, you have mentioned that there are some issues that are beyond the laboratory's control. How do you go about addressing these?

Joshua Lieberman: Yeah, that is I think really important because addressing syphilis requires some multi-specialty approach. So I really think about building collaborations across public health professionals, laboratory medicine practitioners like me, and our patient-facing colleagues across a variety of specialties. So, I think we might think about infectious disease practitioners as one sort of important specialty group, but I also really think of primary care docs in adult, in pediatric medicine, as well as in obstetric cases or you know, obstetricians, as being really important for responding here.

I also think we have to engage organ system specific specialties like neurology and ophthalmology, and even gastroenterology, because you can get these uncommon manifestations in some of these end-organs. I think working together, we can address some of the biological consequences -- biological challenges posed by syphilis. You know, for example, in pregnancy, there about 5% of cases that are missed because patients don't develop an antibody response early enough to be detected at their first obstetric appointment. There are another sort of 34% of congenital cases that occurred despite treating syphilis in pregnancy and you know, in response, to try and deal with some of this case finding, the American College of Obstetricians and Gynecologists now recommends a second test late in pregnancy in the hopes of picking up and treating more of these cases, and that's a mix of public health, lab medicine, and OB care.

In clinical practice, laboratorians can make testing accessible and work to harmonize test results across labs by implementing automated instruments, for example, and making those test results more accessible when patients move between medical systems or get testing at reference laboratories. We can also provide clinical consultations on challenging-to-interpret test results from our gold standard testing. You know, every week, my residents get called for these consults and I think we do a good job in helping ensure that we get what, for example, go right to quantitative RPR for patients with past syphilis, or help find the right test for manifestations of syphilis that are hard to diagnose, like if it occurs in the gut, in the lungs even, or if you get neuroocular involvement.

You know, my hope is that these multidisciplinary efforts can help resolve other limitations. You know, one really heartbreaking example is that nearly half of all congenital cases, even if they got adequate testing, either didn't receive adequate treatment, or in the chart, those CDC authors couldn't find records that the treatment had occurred at all. And that no documented treatment group represents 10 or 11% of all cases of congenital syphilis. You know, my hope is that better education around treatment and congenital disease could have a real impact on this manifestation. You know, in the lab side, I can't address things like social determinants of health or people who avoid healthcare because of prior trauma or experiencing exclusion. I can't really address the crisis in lack of housing or in drug addiction.

These factors all increase the risk for syphilis and they can make it harder to take long courses of antibiotics or lead patients to being lost to follow-up. But I can tell you how worried I am about the major changes to public policy we've seen that threaten to undermine our efforts to combat

syphilis, some of which relate to those social determinants of health. I think, alarmingly in the past few months, we've seen significant disinvestment in public health at the federal level. In April, the entire laboratory branch of the CDC's division of STD prevention was dismantled, really quite suddenly, and very productive contracts they had, and full disclosure, that includes one I helped to develop point-of-care test for *Treponema pallidum*, were canceled. This was only five and a half months before we completed those contracts. The branch has since been reinstated but I am not convinced that the branch will be supported through the next fiscal year. Similarly, I'd say we've seen big reductions, either real or threatened, in federal support for state and local efforts to fight sexually transmitted diseases. Cancelling this funding not only puts patients and the public at risk, but also wastes all the money and effort that we have invested I think so far pretty wisely. Beyond funding, the current federal government's policies, including a recent executive order that really cracked down on homelessness, or other efforts that seem to target or marginalize -- sort of further marginalize minority groups, could really make folks who are at risk for syphilis less likely to seek care, to seek medical care, and that really troubles me. You know, I don't know what this is going to look like moving forward, but I think the sum of current federal policies including those funding reductions, could have profoundly negative consequences for sexually transmitted diseases as well as other important public health priorities. So those are the things that keep me up at night.

Bob Barrett: That was Dr. Joshua Lieberman from the University of Washington in Seattle. He wrote a review article in the September 2025 issue of *Clinical Chemistry* about laboratory strategies to tackle the rapid spread of syphilis. He has been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.