Medical News & Perspectives

Syphilis Has Surged for Reasons That Go Beyond the Pathogen That Causes It

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The flyers for the Syphilis Navigation Connection Helpline (SYNCH) are simple and to the point.

Above a photo of 10 hands, each holding a puzzle piece, the leaflets proclaim in red letters: *Test and We Will Take Care of the Rest!* The helpline's phone number is emblazoned between the slogan and the photo.

SYNCH's acronym is apt. The helpline, a new project of the St Louis County, Missouri, sexual health clinic, promises more than treatment to those it's trying to reach—people with syphilis who are pregnant or could become pregnant. Aiming to reduce congenital syphilis cases, SYNCH offers education, linkage to resources, and partner services.

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Increasingly, public health experts have recognized that testing and treatment alone won't curb the more-than-decade-long rise of US syphilis cases, which in 2022 reached the highest number since 1950, according to the US Centers for Disease Control and Prevention (CDC).

One need look only at the name of a federal task force created in August 2023 for a clue to the complexity of factors contributing to the syphilis resurgence. It's called the National Syphilis and Congenital Syphilis Syndemic (NSCSS) Federal Task Force, chaired by Rachel Levine, MD, assistant secretary for health at the US Department of Health and Human Services (HHS).

Syndemic was coined in the 1990s by University of Connecticut medical anthropologist Merrill Singer, PhD. "Syndemic theory recognizes that social factors create the conditions that support the clustering of diseases and that these diseases interact in a manner that worsens health outcomes," Singer and his coauthor explained in a recent article. "Syndemics theory has helped to facilitate systems-level approaches to disease as a biosocial phenomenon and guide prevention and treatment efforts."

Syphilis clusters with HIV, hepatitis C, and substance use, particularly fentanyl and methamphetamines, Levine noted in an interview with JAMA Medical News. There have been concerns that preexposure prophylaxis (PrEP) for HIV might be linked with an increase in syphilis and other bacterial sexually transmitted infections (STIs) because PrEP would lead to riskier sexual behavior. However, a 2020 study of men who have sex with men in Australia found that their STI positivity was high and increasing *before* starting PrEP. Their STI positivity rate remained high but stable after starting PrEP.

COVID-19 also appears to have contributed to the rising rates of syphilis, but the trend predates the pandemic by several years.

"I think the pandemic…laid bare and made worse the health disparities" resulting from such nonmedical factors as a lack of housing, transportation, economic opportunities, and education as well as food insecurity, Levine said.

"COVID-19 strained an already crumbling public health infrastructure," noted Robert McDonald, MD, MPH, a medical officer in the Division of STD Prevention at the CDC's National Center for HIV, Viral Hepatitis, STD, and TB Prevention. The pandemic increased workloads for local, state, and federal public health agencies, which were already dealing with reduced funding for staff to deal with STIs, he explained. "It's important to build up that workforce."

As a researcher and as medical director of the St Louis County sexual health clinic, Washington University School of Medicine infectious disease physician Hilary Reno, MD, PhD, saw the need to offer syndemic-based, holistic care to people with syphilis, which is why she came up with the idea for SYNCH. What makes SYNCH unique is that it's directed not only toward pregnant people with syphilis but also nonpregnant people with syphilis who could become pregnant in the future, Reno said. The program's staff assess social determinants of health to ensure that the care clients receive is adequate and appropriate. When necessary, SYNCH can link clients to services such as housing and medication to treat substance use disorder, Reno said. Disease intervention specialists, one of whom is also trained as a community health worker, "play a critical role" by making sure that SYNCH clients' sexual partners are also treated, she noted.

The Breadth of the Problem

After reaching historic lows in 2000 and 2001, the rate of primary and secondary syphilis, the most infectious stages of the disease, has increased nearly every year since among men and women and all age groups and in all US regions, according to the CDC. The trend continued apace in 2022, the most recent year for which data are available. The highest rate of reported cases of primary and secondary syphilis that year, 67 per 100 000—or nearly 4 times the national rate of 17.7 per 100 000—was in non-Hispanic American Indian or Alaska Native populations.

In response, the Navajo Health Education Program in February launched the Syphilis Aware initiative, whose tag line is "Protect Yourself, Protect Navajo." The campaign has developed fact sheets and will offer free screening at monthly health expos through the end of the year.

The second-highest rate of cases per 100 000 population, 44.4, was in the Black population, followed by 30.2 in the Native Hawaiian or Other Pacific Islander population, 25 in the multiracial population, 18.6 in the Hispanic or Latino population, 10.2 in the White population, and 4.9 in the Asian population. In 2022, 207 255 cases of syphilis were reported in the US, an increase of 17.3% in just 1 year, according to the CDC. Of those cases, 3755 were congenital syphilis, linked to 282 stillbirths and infant deaths.

At a time when perinatal infections such as HIV and hepatitis B have been declining, the US congenital syphilis rate in 2022, which was 102.5 cases per 100 000 live births, represented a nearly 31% increase over 2021 and was the highest reported since 1991. Rates of primary and secondary syphilis in women aged 15 to 44 years increased in 35 states from 2021 to 2022, the CDC reported. And yet, Levine noted, "congenital syphilis is completely preventable."

Other countries are experiencing similar increases in syphilis, which, left untreated, may lead to potentially fatal complications in multiple organs years after infection. Worldwide, new syphilis cases rose by more than 1 million in 2022 to 8 million, according to a May 21 report from the World Health Organization (WHO). The highest increases occurred in the Americas and Africa, the report noted. In 2022, WHO member states had set a goal of reducing total adult syphilis cases 90% by 2030.

Out of Sight, Out of Mind?

In 1999, the CDC launched the National Campaign to Eliminate Syphilis from the United States. The program set a deadline of 2005 for reducing the country's number of primary and secondary cases of syphilis to 1000 and raising the proportion of counties without any cases to 90%.

That didn't seem like a pie-in-the-sky goal at the time. After all, the rate of primary and secondary syphilis had fallen approximately 90% from 1990 through 2000, according to the CDC. In 1999, there were 6617 reported cases of primary and secondary syphilis in the US, and that number dropped to 5979 in 2000.

But syphilis cases began to creep back up in 2001. The problem was that the shrinking syphilis numbers in the 1990s meant many clinicians didn't give the STI much thought when cases began increasing, McDonald said.

"Toward the end of the last century, we were so close to syphilis elimination," he explained. "It became something that we weren't screening for, that we weren't testing for, that we weren't thinking about. For most of us, when we were coming up through training, we didn't see syphilis." As a result, clinicians often don't "even think about it on the differential diagnosis," McDonald noted.

Many patients don't notice the main symptom of primary syphilis infection: small painless sores on the genitals, anus, or wherever else the bacterium *Treponema pallidum* entered the body. Often, neither do their health care practitioners.

"We know that to address syphilis, you need to be testing for syphilis," McDonald said.

Testing, Testing, Testing

Lack of timely testing and adequate treatment contributed to 88% of US congenital syphilis cases in 2022, according to an article McDonald coauthored in November in the *Morbidity and Mortality Weekly Report* (*MMWR*). As of that month, 8 states did not require a syphilis test at the first prenatal visit, and only 6 recommended testing all pregnant individuals when they deliver, a point at which syphilis can still be passed from untreated mother to newborn.

Because of the rapidly increasing congenital syphilis rates, the American College of Obstetricians and Gynecologists (ACOG) in April updated its recommendation about screening for syphilis in pregnancy.

Previously, ACOG recommended universal first-trimester screening and additional screening for pregnant people who are at risk or live in areas with high rates of syphilis. However, that approach required that clinicians be able to take patient histories to accurately assess risk and to know whether their area has high syphilis rates. The updated ACOG practice advisory instead recommends that obstetric care professionals screen all pregnant individuals at the first prenatal care visit, during the third trimester, and at birth.

Because many patients receive limited prenatal care, though, Levine's federal syphilis task force has promoted testing pregnant people for syphilis beyond traditional prenatal care settings, including at substance use facilities, harm reduction programs, and emergency departments.

Ramping up testing is easier said than done, though. As McDonald noted, syphilis isn't usually top of mind for clinicians. Plus, he pointed out, "we haven't had that many advances in testing for syphilis."

Urine specimens can be used to test for chlamydia, gonorrhea, and trichomoniasis, and oral swabs can be used to test for HIV. But a blood draw is required to test for syphilis. "A lot of easier tests are out there for other organisms," McDonald said.

Plus, "syphilis is not a positive or negative situation," Reno noted. "If you have a past history of syphilis, you can still end up with a positive test." If someone with a history of being treated for syphilis tests positive, a second test is done to determine whether or not they've been reinfected.

A rapid point-of-care test for syphilis and HIV that requires only a fingerstick has been available for a few years, but it too can yield false-positive results for syphilis, according to Reno. "I've seen these tests used by street medicine groups," she said. She explained that if someone who is unhoused tests positive for syphilis on a rapid test, they'll receive an injection of penicillin G benzathine on the spot with the hope they'll come to a clinic for a full blood workup.

Lack of Treatments

The preferred treatment for syphilis hasn't changed in 80 years, and it's been in short supply since at least last summer, a situation that is expected to continue until the end of this year. Pfizer, the only US supplier of penicillin G benzathine, which it markets as Bicillin L-A, says it hasn't been able to keep

up with demand. Penicillin G benzathine injection is the only effective syphilis treatment for pregnant people and infants with congenital syphilis. Nonpregnant people can be treated with doxycycline pills for 2 to 4 weeks, compared with 1 or 3 benzathine penicillin G shots depending on whether the infection is in its early or later stages.

Because of the shortage, the US Food and Drug Administration (FDA) in January allowed temporary importation of benzathine benzylpenicillin (Extencilline), manufactured in Italy for a French pharmaceutical company. Benzathine benzylpenicillin is another name for penicillin G benzathine. Extencilline is not FDA approved, but it is authorized and marketed in other countries and is equivalent to Pfizer's product.

Although these drugs are highly effective, "we need more advances," including vaccines against syphilis and other STIs, Levine noted. The HHS recently hosted a workshop with National Institutes of Health scientists to discuss the development of new syphilis treatments.

Putting PEP Into Preventing Syphilis

One recent development has been clinical trials showing that 200 mg of doxycycline, taken within 72 hours of condomless sex, can reduce the risk of syphilis, chlamydia, and gonorrhea in cisgender men who have sex with men and in transgender women who have sex with men. (The reason clinical trials have not found doxycycline postexposure prophylaxis, or doxyPEP, to be effective in cisgender women might simply be because those assigned to take it didn't, suggested an article in December.)

Clinical trial results published in 2023 demonstrated that doxyPEP, compared with usual care, reduced the combined incidence of the 3 bacterial STIs by two-thirds in cisgender men and transgender women who have sex with men. "Think of it as a morning-after pill but for bacterial STIs instead of pregnancy," notes the website for Howard Brown Health, a nonprofit LGBTQ health care and social services provider in Chicago.

The FDA hasn't approved doxyPEP, but a number of public health agencies, including the CDC, the Los Angeles County Department of Public Health, the New York City Department of Health and Mental Hygiene, and the Virginia Department of Health, have developed guidelines for its use.

The CDC on June 6 published guidelines in *MMWR* for clinicians on counseling patients about doxyPEP. The guidelines recommend discussing doxyPEP with men who have sex with men and transgender women with a history of at least 1 bacterial STI in the previous 12 months. Even if men who have sex with men and transgender women don't have a history of a recent bacterial STI, clinicians could discuss doxyPEP with them if they're going to participate in activities that could increase the likelihood of STI exposure, the guidelines note. After counseling patients, clinicians should write a prescription for self-administration of doxycycline within 72 hours of sex.

But some of the same obstacles that deter testing and treatment for syphilis could also block access to doxyPEP, cautioned the authors of an article published in February. "Although this intervention could significantly reduce incident STIs, its implementation has the potential to perpetuate existing inequities," they wrote.

Meet Them Where They Are

As far as Kimberly Stanford, MD, knows, her emergency department at the University of Chicago Medicine was the first in the US to offer universal screening for syphilis, which began in May 2019.

Fewer and fewer people have a primary care clinician, Stanford explained. "It's not their fault. It's the system failing them." That's why the emergency department seemed like a logical place to screen patients for syphilis, she said, regardless of whether they're seeking help for a sprained ankle or an unusual vaginal discharge. "This is where people are coming for their health care."

Compared with the 7 months before their emergency department implemented universal syphilis screening, the number of screening tests more than tripled in the 7 months afterward, Stanford and coauthors recently reported.

Most patients have left the emergency department by the time their syphilis blood test results become available, Stanford said. Still, she noted, 70% to 80% of those found to have syphilis are treated, and "most of them come in and get treatment from us."

At the UAB (University of Alabama at Birmingham) Hospital, Lauren Walter, MD, MSPH, hopes to begin "prioritized" syphilis testing in the emergency department as soon as the institutional review board approves. "It's just more cost-effective" than universal screening, she explained.

Until now, when patients came to the emergency department with symptoms suggestive of an STI, they might get a urine test to check for trichomoniasis, Walter said. "It's not really been on our radar to consider or check for syphilis."

She recently coauthored a 30-day retrospective study of patient visits to her emergency department that was designed to assess the potential benefit of targeted syphilis screening. Walter and her collaborators reviewed electronic medical records (EMRs) to see whether patients with predetermined syphilis "flags" were tested for the disease. The so-called flags were a history of an STI, the patient's chief concern or the triage nurse's summary of it that suggested an STI, or a positive pregnancy test.

Of 5537 encounters during September 2022, 455 visits were flagged, but an order was written for a syphilis test in fewer than a third of the flagged encounters. Of the 120 syphilis screening tests ordered, 29 (24.2%) came back positive. Some clinicians are probably more likely to order syphilis testing than others, Walter noted. Under the proposed plan, the EMR will automatically flag patients who are at risk for syphilis and order a screening test for them, she explained.

A linkage coordinator will attempt to contact patients who have positive results, and the county health department will also be notified, Walter said. Unlike Stanford's emergency department in Chicago, Walter's is leaving syphilis treatment to the county health department and others. "Our capacity to take care of nonemergent issues is often limited," she noted.

Common Threads

Reno knows that stemming the rise in syphilis requires more than just determining that someone is infected and then "throwing Bicillin at them."

She recently coauthored a study of people who delivered infants with congenital syphilis between December 2015 and June 2022 in a Missouri hospital system. Half of the mothers had received inadequate prenatal care, and more than 40% had a history of substance use, which correlated with inadequate prenatal care, Reno and her coauthors reported.

Missouri's data are far from unique. A study of pregnant people with syphilis in Arizona and Georgia during 2018 to 2021 found that those who transmitted the

infection to their offspring were more likely to have used substances than those who did not transmit it, researchers reported in *MMWR* in 2023. About half the people who used substances during pregnancy and transmitted syphilis to their fetus or newborn had late or no prenatal care, the researchers found.

Syphilis is spread mainly through sexual contact and, rarely, through blood transfusions; unlike HIV, it is rarely transmitted by sharing contaminated injectable drug equipment. Still, syphilis clusters with substance use, but for less obvious reasons. For example, an altered state of consciousness from substance use can lead to "a potential increase in sexual risk behaviors," McDonald explained. And people who use substances typically engage in risky sexual behaviors with partners who also use substances, noted Reno, coauthor of the CDC's most recent STIs treatment guidelines, published in 2021. "Those aren't just factors that exist alone in a population. They are interacting with each other in a not great way," she said.

As chair of the federal syphilis task force, Levine has traveled the country to learn about the challenges local public health officials like Reno are facing with the surging STI. Among other places, she recently visited Cahokia Heights, Illinois, which sits directly across the Mississippi River from St Louis, and the Navajo Nation, whose seat of government is in Window Rock, Arizona. Three-quarters of Cahokia Heights' residents are Black people, while virtually all those who live on the sprawling Navajo Nation Reservation are Native American people. Although these are different populations in different settings, Levine said she couldn't help but notice that the 2 communities are lacking in many of the same social determinants of health, including adequate housing and nutritious food. "Syphilis," she pointed out, "is yet another health equity issue." ■

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Correction: The article was updated on June 27, 2024, to reflect the CDC's final clinical guidelines, published on June 6, 2024, on the use of doxyPEP for preventing bacterial STIs such as syphilis.

Conflict of Interest Disclosures: Dr Reno reported receiving research funding from the National Institutes of Health and the St Louis County Department of Health and giving paid talks for the Clinical Training Center for Sexual and Reproductive Health and Prime, a continuing medical education company. She also serves on the boards of the American Sexually Transmitted Diseases Association and its journal, *Sexually Transmitted Diseases*. Dr Stanford reported receiving grants from the National Institute of Allergy and Infectious Diseases, the Chicago Department of Public Health and the Health Resources and Services Administration, and the Emergency Medicine Foundation and that the Gilead FOCUS program provides some funding for syphilis screening in her emergency department. Dr Walter reported that the Gilead FOCUS program will support the anticipated syphilis screening at the UAB emergency department. No other disclosures were reported.

Note: Source references are available through embedded hyperlinks in the article text online.