Resurgence of Syphilis in the US—USPSTF Reaffirms Screening Guidelines

Erin H. Amerson, MD; Herbert B. Castillo Valladares, MD, MHS; Kieron S. Leslie, MD

**Since its modern-day nadir** of 5979 cases per year, or 2.1 cases per 100,000 population, in 2001, primary and secondary (PS) syphilis incidence has rapidly increased. In 2019, 38,992 cases, or 11.9 cases per 100,000, were reported, more than a 5-fold increase. The United States Preventive Services Task Force (USPSTF) currently “recommends screening for syphilis infection in persons who are at increased risk for infection” (A recommendation). The recommendation applies to asymptomatic, nonpregnant adolescents and adults who have ever been sexually active and is based on findings that the benefits of screening outweigh the harms. Because dermatologists are among the frontline health care professionals in the fight against syphilis, the USPSTF recommendation, supported by an updated evidence report and systematic review, presents an opportunity to update the dermatology community regarding recent trends in syphilis epidemiology, clinical presentation, testing, and treatment.

**Epidemiology and Risk Stratification for Screening**

First, there should be focus on the recommendation to screen patients at high risk for syphilis. To screen is to routinely test regardless of symptoms. While the term high risk is likely intentionally vague to allow for broad implementation of screening at the clinician’s discretion, we outline herein the epidemiologic data guiding who may benefit most from screening.

Syphilis is more common in men. In 2019, 83% of PS syphilis cases occurred in men, and men who have sex with men (MSM) were disproportionately affected, as 57% of reported PS cases occurred in MSM. Transgender women likely experience syphilis infection at similar rates to MSM, though surveillance data are limited among this group. The rate of syphilis in MSM has rapidly increased. During 2016 to 2020, the number of cases among MSM increased 11.2% (16,155 in 2016 to 17,968 in 2020), though recent data suggest that this rise may be leveling off. However, the plateau may reflect a COVID-19-related diversion of public health resources at county, state, and federal levels affecting surveillance and reporting. Meanwhile, the number of PS syphilis cases in women has nearly tripled between 2015 and 2019. Downstream of the rise of syphilis in women is an uptick in the incidence of congenital syphilis. In 2020, 2148 cases of congenital syphilis were reported, which represent near tripling of cases compared with 641 cases in 2016. Given that 76% of untreated syphilis cases in pregnancy result in an adverse outcome, including miscarriage, stillbirth, neonatal death, low birth weight, or a child with stigmata of congenital syphilis, this alarming trend puts both mothers and infants at risk.

In addition to gender and sexual orientation, dermatologists should recognize considerable racial and ethnic disparities in syphilis incidence. Black women and men alike, and particularly Black MSM, are at increased risk. In 2020, the highest rate of reported cases of PS syphilis was among non-Hispanic Black or African American persons (34.1 cases per 100,000). Among women, non-Hispanic American Indian or Alaska Native women had the highest rate of reported cases of PS syphilis (21.3 per 100,000). This parallels the highest rates (190.6 per 100,000) of congenital syphilis found in American Indian and Alaska Native persons. These disparities are likely associated with the well-documented barriers to quality health care access in Black and Indigenous populations, as well as differences in social determinants of health, which have been shown to influence the incidence of syphilis of historically marginalized racial and ethnic groups at a local level. Furthermore, racial segregation can compound increasing syphilis rates by isolating sexual networks in specific communities. Dermatologists need to be aware of the rapidly shifting demographics of syphilis while balancing the risk of further stigmatization in already marginalized groups.

Geographically, the American West and Southeast currently have the highest rates of PS syphilis as of 2020 (16.7 and 13.2 per 100,000, respectively), and while urban counties consistently report the highest incidence rates, rates among some rural jurisdictions are increasing, among women in particular. Dermatologists should be aware of local epidemiologic trends to guide their screening practice. Finally, persons living with HIV infection, those with methamphetamine or opioid use disorder, young adults, and those with a history of incarceration, transactional sex, or military service represent additional at-risk groups.

**Testing and Screening**

Some laboratories have adopted a “reverse sequencing” algorithm in recent years, meaning that the initial study is an automated treponemal test (typically an enzyme immunoassay or chemiluminescent immunoassay) rather than a nontreponemal (RPR or VDRL) test. There are a few important points for clinicians to understand about reverse sequencing. First, this change owes to the development and adoption of inexpensive, rapid-throughput treponemal assays—in other words, cost and ease of testing, not test superiority, is driving this shift in practice. Second, while treponemal tests have increased sensitivity in early primary syphilis compared with nontreponemal tests, they remain positive for life in most patients and therefore are not useful in patients who have previously been diagnosed and treated for syphilis. In the reverse-
sequencing algorithm, if a patient has a positive treponemal test, a nontreponemal test is then performed to confirm an active case. A nontreponemal test should ideally be repeated on the day of treatment, and a 4-fold decrease in the RPR titer is expected over 12 months to signify a successful treatment response.4

The recommended frequency of screening is ambiguous, though more specific guidelines for certain groups have been suggested. For example, MSM and persons living with HIV infection should be screened at least annually, or more frequently (every 3 to 6 months) if they have high-risk behaviors and/or are taking HIV pre-exposure prophylaxis.10 Pregnant women should be screened at their first prenatal visit, and women at high risk (high local endemicity, multiple sex partners, methamphetamine or heroin use, transactional sex, late entry into prenatal care, incarceration of woman or her partner, and unstable housing or homelessness) should be screened at the beginning of the third trimester and again at delivery.4,11

Syphilis lateral flow point-of-care tests, which can give a result in minutes with a drop of blood, can eliminate the need to wait for a result in patients who are at risk of being lost to follow-up. These tests are approved by the US Food and Drug Administration and commercially available, though data are lacking regarding how widely these tests are being adopted in US health care settings.

Finally, patients testing positive for syphilis should be offered other sexually transmitted infection and HIV testing. Women should receive a pregnancy test. Diagnosing a sexually transmitted infection such as syphilis also presents an opportunity to discuss pre-exposure prophylaxis for HIV and vaccination for hepatitis B, meningococcus, and monkeypox in patients at high risk.

Clinical Characteristics

While syphilis has long been known as the “great imitator,” reports of the myriad clinical presentations of the disease continue to expand. First, dermatologists must recognize that the painless, rubbery, ulcerating chancre of primary syphilis may occur on extragenital sites, most commonly the mouth or anus.12 It may also present as multiple ulcerations.12,13 Syphilis testing should be offered to anyone presenting with a new papulosquamous rash or exanthem. Increasingly, nonpapulosquamous morphologies, including pustular, crusted or ecchymalike (so-called lues maligna),14 prurigo nodulike, or targetoid morphologies, have been reported.15 Dermatologists should also be aware that ocular and neurosyphilis may present concurrently with PS syphilis. Given that neurosyphilis can lead to permanent deficits, including vision or hearing loss, and must be treated with 2 weeks of intravenous penicillin (contrasting with a single intramuscular dose of penicillin G given for nonneurosyphilis), dermatologists should ask any patients who present with syphilis about hearing or vision changes, headaches, stiff neck, or other neurologic symptoms.16

Treatment and Prophylaxis

Most cases of PS syphilis without neurologic involvement will respond to treatment with 2.4 million units of intramuscular benzathine penicillin G given in a single dose. There is no longer a recommendation to treat PS syphilis in persons living with HIV infection with more than 1 dose. Nonpregnant patients who are allergic to penicillin may be treated with doxycycline, 100 mg, twice daily for 14 days. Emerging macrolide-resistant infections mean that azithromycin is no longer a recommended treatment. Patients should be warned about the Jarisch-Herxheimer reaction, which manifests as fevers and myalgias within the first 24 hours of treatment.2 Patients with late latent or tertiary syphilis require 3 doses of intramuscular benzathine penicillin G administered 1 week apart.4

Doxycycline as pre-exposure and postexposure prophylaxis is a potential future direction in syphilis prevention. Daily doxycycline, 100 mg, administered prophylactically reduced the combined odds of syphilis, gonorrhea, and chlamydia infection in a group of HIV-infected MSM. An open-label study of MSM showed that postexposure prophylaxis with doxycycline, 200 mg, given within 24 hours after a sexual encounter resulted in a 73% reduction in the risk of syphilis over a mean follow-up period of 8.7 months.4 While the routine use of doxycycline as pre-exposure and postexposure prophylaxis is not yet recommended, larger studies are being conducted to assess the efficacy of doxycycline as postexposure prophylaxis as a potential option for syphilis prevention in high-risk groups.

Conclusions

Syphilis epidemiology is rising in the US, and trends are particularly troublesome among high-risk groups. The US Centers for Disease Control and Prevention may be underestimating the true prevalence of syphilis and other sexually transmitted infections owing to diversion of resources during the COVID-19 pandemic. Dermatologists should increase vigilance and have a low threshold to test any patients with orogenital ulcerations or rash. Additionally, screening asymptomatic, high-risk populations in accordance with the USPSTF recommendation should be considered.

ARTICLE INFORMATION

Author Affiliations: Department of Dermatology, School of Medicine, University of California, San Francisco (Amerson, Castillo Valladares, Leslie); Department of Dermatology, Zuckerberg San Francisco General Hospital and Trauma Center, San Francisco, California (Amerson, Leslie).

Corresponding Author: Erin H. Amerson, MD, Department of Dermatology, School of Medicine, University of California, San Francisco, 1701 Divisadero St, San Francisco, CA 94115 (erin.amerson@ucsf.edu).

Published Online: September 27, 2022. doi:10.1001/jamadermatol.2022.3499

Conflict of Interest Disclosures: None reported.

REFERENCES


3. Henninger ML, Bean SI, Lin JS. Screening for syphilis infection in nonpregnant adults and


