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# Resurgence of syphilis in the US

Abstract: Despite advances in screening and treatment for syphilis, the US has seen increased incidence of the disease in the past decade. This article gives an overview of incidence, risk factors, clinical manifestations, assessment, screening, treatment, and prevention of syphilis.

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ohn Carlo, a 34-year-old who identifies as a male, arrives in the primary care clinic because he is having trouble keeping up with the physical labor required for his job as a building maintenance supervisor. He has been very tired over the last several weeks and reports that he believes he has arthritis like his father because his joints are hurting. He has taken ibuprofen with some improvement, but it upsets his stomach. He indicates that he sometimes smokes marijuana when he has trouble sleeping because of the pain. Further questioning reveals that he has frequent headaches and a "weird rash" on his hands and genital area. On exam, the NP notes ulcerous plaques on his upper lip with submandibular lymphadenopathy, a painless macular rash with scarred lesions on his penis, and a maculopapular rash on his hands.

Mr. Carlo is currently sexually active with two male partners. One of his partners is currently on preexposure prophylaxis (PrEP) medication for HIV prevention. All three partners are HIV-negative. The NP orders a complete blood cell count, HIV test, rapid plasma reagin (RPR), nucleic acid amplification test (NAAT) for gonorrhea/chlamydia, and a hepatitis panel. The NP calls Mr. Carlo the following day to let him know that his RPR and subsequent Treponema pallidum particle agglutination (TP-PA) tests are positive indicating current syphilis infection. HIV, gonorrhea, chlamydia, and hepatitis tests are all negative. The NP explains to Mr. Carlo that he has secondary syphilis, which is sexually transmitted and contagious.

\**Case study is a compilation of details from several patients.* 

Despite advances in screening and treatment for syphilis, there is a marked increase in the incidence of syphilis in the US.<sup>1</sup> Changes in social and behavioral perception of risk are contributing to the epidemic, and a steady drop in the incidence of syphilis is only possible through an expanded prevention approach from both public and private health arenas as well as community members.<sup>1</sup>

Keywords: chancre, sexually transmitted infections, STIs, syphilis, syphilis screening

## What is syphilis?

Syphilis is a sexually transmitted disease caused by Treponema pallidum, a slow-growing bacterium that usually takes 2 to 3 weeks to begin manifesting symptoms. It can take up to 3 months for symptoms to develop and initial symptoms may not be recognized.<sup>2</sup> It is passed from person to person by direct contact with a syphilitic sore, known as a chancre (pronounced shanker).<sup>2</sup> Chancres can occur on or around the external genitals, in the vagina, around the anus, in the rectum, or in or around the mouth.<sup>2</sup> Transmission of syphilis can occur during vaginal, anal, or oral sex as well as with any other genital contact and sharing of sex toys.<sup>2</sup> Sharing food and drink or towels and toilet seats with people who have syphilis is considered safe, as is hugging, holding hands, coughing, or sneezing.<sup>3</sup> Venereal (sexually transmitted) syphilis can only be transmitted by direct contact with infected tissue.<sup>3</sup>

#### Incidence of syphilis

The US has seen an increase in the incidence of syphilis in the past decade.<sup>1</sup> Most cases are among men who have sex with men (MSM), but rates of the disease in premenopausal women and congenital syphilis (disease present from birth) have also increased.<sup>1</sup> The resurgence has occurred despite availability of prevention programs and effective treatment. Death from syphilis is rare, but the case-fatality rates of babies born with syphilis is 6.5%.<sup>1</sup> In 2000, the rate of infection was 2.12 per 100,000. The incidence rate climbed to 9.5 per 100,000 in 2017. Incidence is significantly higher for males (16.9 per 100,000) versus females (2.3 per 100,000).<sup>1,4</sup>

The number of primary and secondary syphilis cases increased 14% to more than 35,000 cases between 2017 and 2018.3 In 2017-2018, the CDC reported a 36% increase in syphilis among women of childbearing age, and a 40% increase in congenital syphilis cases.<sup>3</sup> In 2013, there were 362 documented cases of congenital syphilis. In 2017, that number increased by 153%, to 918 cases.<sup>1,3</sup> In 2019, newborn deaths related to congenital syphilis rose from 77 to 94, an increase of 22%.<sup>3</sup> In 2018, Dr. Jonathan Mermin, Director of the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention with the CDC, cautioned during the National STD Prevention Conference, "We are sliding backward. It is evident the systems that identify, treat, and ultimately prevent sexually transmitted diseases are strained to near-breaking point."3

#### What are the risk factors?

Healthcare providers should always ask about risk factors for any sexually transmitted infection (STI) including syphilis.<sup>5</sup> Persons are at a higher risk for contracting syphilis when they have unprotected sex (sex without using a condom or other barrier), have sex with multiple partners, or have sex with someone who has HIV.<sup>5</sup> Persons who have been incarcerated, are HIV-positive, MSM, and sex workers are at higher risk of contracting syphilis.<sup>5</sup> The disease may also be passed from an infected mother to her unborn baby.<sup>5</sup>

#### Resurgence of syphilis

The resurgence of syphilis in the US is attributed to sexual behavior, HIV coinfection, having multiple sex partners, practicing unsafe sex, and illicit drug use.<sup>1</sup> Unprotected anal intercourse is one of the greatest risk factors for contracting syphilis. In their study, Rice et al. reported a majority of MSM conveyed having unprotected anal sex (90%) in their lifetime.<sup>6</sup> There is an increased risk of epithelial tears to the rectal mucosa attributed to the lack of lubricating capability and elasticity. Being highly vascularized, the rectum creates a route for pathogens to enter the blood stream.<sup>1,6</sup>

The advances in HIV treatment, as well as the use of PrEP and postexposure prophylaxis (PEP) may have negatively impacted STI preventive behaviors, according to Schmidt et al. Paz-Bailey et al. reported an increase in condomless sex among HIV-positive MSM.<sup>1,7</sup> Schmidt et al. reported MSM with multiple partners often cluster in sexual networks that may increase the risk of exposure to STIs, and that MSM with six or more partners were three times more likely to have syphilis compared with those with a single partner.<sup>1</sup>

When Mr. Carlo returns to the clinic, the NP stresses the importance of treatment to prevent further progression and transmission. The NP helps him role-play notifying his sexual partners so that they also can be tested and receive treatment if necessary. He is treated with 2.4 million units of penicillin G I.M. She advises abstinence from sexual contact with any partner until the chancres are completely healed.<sup>4</sup> They discuss the decreased inhibitory effect of drug use on sexual decision-making and associated risks.

The increased use of illicit drugs is a risk factor in the resurgence of syphilis.<sup>8</sup> Drugs may lead to altered judgment, lowered inhibitions, increased impulsive behaviors, enhanced sexual pleasure, and are associated with highrisk behaviors including condomless intercourse.<sup>8</sup>

HIV and syphilis have a cooperative relationship; the risk of contracting HIV increases fivefold when either partner has syphilis. Transmission and acquisition of HIV is increased when syphilis lesions are present.<sup>9</sup> Additionally, immunosuppression from HIV may allow *T. pallidum* to invade the host more readily.<sup>1</sup> Tilchin et al. determined that the risk of an HIV diagnosis following a syphilis or gonorrhea infection was 13.5% among MSM.<sup>10</sup>

The NP explains to Mr. Carlo that current research indicates that MSM have a 3.62 times higher HIV risk compared with men who do not have sex with other men after they have had a syphilis infection, and that 1 in 10 syphilis or gonorrhea diagnoses among MSM is followed by an HIV diagnosis within 2 years.<sup>10</sup> She tells him that these results add to previous evidence that syphilis infection increases the risk of acquiring HIV. She discusses the window associated with HIV testing and recommends followup testing in 3 months. She recommends that Mr. Carlo begin PrEP against HIV, following guidelines that PrEP be offered to any patient diagnosed with primary, secondary, or latent syphilis who is HIV-negative.<sup>10</sup> She further recommends that Mr. Carlo be tested regularly for STIs and routinely use condoms with all sexual partners. Reinfection is likely if infected partners are left untreated.

#### Stages of syphilis

Syphilis develops in four stages: primary, secondary, latent, and tertiary. Primary syphilis may last 3 to 6 weeks and progresses to secondary and latent and possibly tertiary syphilis if treatment is not received.<sup>4</sup> Early latent disease is classified as infection acquired within the previous 12 months, and late latent infection describes an infection that occurred more than 12 months ago.<sup>4</sup> Tertiary syphilis is rare and may occur if syphilis is not treated, possibly appearing 10 to 30 years after infection was initially acquired. It can affect multiple organ systems and can be fatal.<sup>4</sup>

**Primary syphilis manifestations.** Syphilis has been referred to as "the great imitator" for its difficulty with diagnosis, as rash and lesions often resemble other infectious conditions.<sup>2</sup> The incubation period from contact with syphilis to the first symptom is 10 to 90 days, with most symptoms appearing around day 21.<sup>2</sup> The initial symptom is a single (possibly more than one) round, firm, usually painless lesion called a chancre, occurring at the site of entry to the body and may be difficult to detect if in the vagina or anus (see *Penile chancre: Primary syphilis*).<sup>2</sup> The chancre lasts 3 to 6 weeks and heals

Penile chancre: Primary syphilis



with or without treatment.<sup>2,4</sup> Regional lymphadenopathy may occur in primary disease and last for months after the primary lesion has resolved.<sup>11</sup>

Secondary syphilis manifestations. If primary syphilis is not diagnosed, the disease progresses to secondary syphilis where symptoms include a nonitchy, rough, red or brownish skin rash, often on the palms of the hands and soles of the feet, but may appear on other parts of the body and may be very faint (see Palmar lesions: Secondary syphilis).<sup>2,4</sup> Other symptoms include sores in the mouth, vagina, or anus which may manifest as the chancre is still healing or appear several weeks later. Large wartlike lesions may occur in the mouth, axilla, or groin area. Flulike symptoms of fever, lymphadenopathy, sore throat, headache, myalgia, fatigue, patchy alopecia, and weight loss may also occur.<sup>2,4,11</sup> Symptoms from untreated secondary syphilis may last anywhere between 4 weeks and 6 months.<sup>2,11</sup> These symptoms usually resolve with or without treatment but will progress to latent or possibly tertiary stages, if left untreated.<sup>2</sup>

*Latent syphilis manifestations.* In the latent stage of syphilis, the body shows no physical signs of disease. Early latent syphilis is where infection occurred within the past 12 months, and late latent syphilis is where infection occurred more than 12 months ago, or is of unknown duration. The disease may progress if no treatment is received.<sup>2</sup> If early latent syphilis is untreated, up to 25% of patients may experience a relapse of secondary symptoms, and sexual transmission may still occur.<sup>11</sup>

*Tertiary syphilis manifestations.* Most people do not develop tertiary syphilis; however, if untreated, syphilis can potentially lead to neurologic complications, hearing loss, and blindness.<sup>1</sup> The disease can affect the heart, brain, and nervous system and may eventually cause death.<sup>1</sup>

Neurosyphilis occurs when the bacteria invade the nervous system, a process that can occur at any stage of the disease. Symptoms include headaches, altered muscle movements, paralysis, sensory impairment, and dementia. Another potential risk is for ocular syphilis which can occur at any stage and can cause vision changes and blindness. Clinicians should ask any patient at risk for syphilis about visual changes.<sup>1,4</sup>

#### Screening for syphilis

Syphilis infection results in substantial morbidity and mortality. Essential questions an NP should ask patients at least once a year include: Have you ever had sex, either vaginal, oral, or anal (rectal)? Have you had sex in the past 12 months? Do you have sex with men, women, or both? In the past 12 months, how many sexual partners have you had?<sup>12</sup> It is important to remember that adolescents and adults may have sexual partners whom they may not consider to be boyfriends or girlfriends, and therefore screening questions should be specific, which may be asked in person or via an intake form.<sup>12</sup>

Gender identity may change over time, so it is important to ask patients about their gender assignment at birth and current gender identity. All sexually active adolescents and adults should be counseled on the use of



condoms and contraception regardless of their sexual orientation.<sup>12</sup>

The CDC suggests focusing on "sexual health" rather than "sexual disease" to help patients feel more comfortable discussing sexual practices with their provider, in addition to recommending the "Five Ps" strategy for sexual histories (partners, practices, pregnancy prevention, protection from STIs, and past history of STIs), emphasizing simple language and open-ended questions.<sup>1</sup> Patients should be counseled on proper fitting of a condom and advised that condoms are not as effective at preventing infections that are transmitted through lesions, such as syphilis, if the lesion is not covered by the condom.<sup>1</sup>

#### Guidelines for syphilis screening

The United States Preventive Services Taskforce (USPSTF) recommends screening for all nonpregnant adults and adolescents who are at increased risk of syphilis infection. The CDC recommends screening for those with a history of incarceration, sex workers, those living in areas with high prevalence rates, and men under age 29. MSM, gender-diverse individuals (depending on sexual behaviors and exposure), and people with HIV should be screened at least annually.<sup>13</sup> The net benefit of screening these patients is substantial (see *Guidelines for syphilis screening*).<sup>14-16</sup>

The USPSTF also recommends early screening for syphilis in all pregnant women.<sup>17</sup> In addition to screening at the first prenatal visit, the CDC recommends that highrisk pregnant women be rescreened for syphilis early in the third trimester and again at delivery.<sup>4</sup> High-risk pregnant women may include those living in an area with a high syphilis morbidity rate; those with no prior syphilis testing; those who are uninsured, low-income, homeless, or unstably housed; those with history of STI during the pregnancy; those who have been incarcerated or whose sex partner has been incarcerated; those who use drugs; and women who exchange sex for money or drugs.<sup>9,11</sup>

#### Testing

In addition to screening recommendations outlined above, testing for syphilis should be performed on anyone showing signs or symptoms of infection.<sup>18</sup>

There are two types of tests used to detect syphilis. The first type includes nontreponemal tests (NTTs), such as the RPR and Venereal Disease Research Laboratory (VDRL) serology tests. NTTs are not specific to syphilis because they detect the presence of antibodies to cardiolipins, which are produced because of cellular damage

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associated with infection. Quantitative titers from NTTs can help differentiate those with active disease from those with adequate treatment, but false positives are still possible and may be associated with pregnancy. NTTs are not sufficient to diagnose syphilis infection and require additional testing to confirm the patient's infection status.<sup>9,11</sup> NTT quantitative titers are also used to assess for response to treatment and/or potential reinfection.<sup>16</sup>

Treponemal tests (TTs), such as *T. pallidum* particle agglutination (TP-PA) and fluorescent treponemal antibody absorption (FTA-ABS), detect IgM and IgG antibodies specific to *T. pallidum*. TTs can confirm previous infection with syphilis but they do not differentiate between previous infection and active disease as they usually remain positive for life regardless of treatment.<sup>9,11</sup>

There are two testing algorithms being used in practice, each of which have benefits and limitations.<sup>15</sup> The first is the classic algorithm in which an NTT test is first administered, and if positive, a follow-up with a TT is completed. The reverse sequence algorithm starts with a TT, which if positive, is followed by an NTT.9,11 Discordant results are resolved with a different TT than used with the initial screen, consideration of risk factors, and clinical impression.<sup>16</sup> The decision about which algorithm is used depends on volume, cost, population served, and syphilis risk in the population.<sup>15</sup> Early syphilis infection may be missed using either algorithm but that possibility is less likely with the reverse algorithm; however, the reverse algorithm produces more false positives related to previous infections, adding to the cost of follow-up.15 Providers should be aware of which algorithm is being utilized at their site of practice and clinical assessment and evaluation should always be considered when interpreting testing results.9,11

#### Treatment

Treatment with a single dose of long acting benzathine penicillin G, 2.4 million units I.M. is recommended by the CDC for primary, secondary, and early latent syphilis in adults and is usually curative for these stages (see *Syphilis stages and treatment*). Sexual partners within the last 90 days should also be treated presumptively even if testing is negative.<sup>16</sup> NTT quantitative titers and clinical evaluations should be repeated at least 6 and 12 months after treatment for syphilis to assess for adequate treatment response and/or potential reinfection.<sup>16</sup>

For late latent syphilis or latent syphilis of unknown duration, affected persons will require dosing of benzathine penicillin G 2.4 million units I.M. weekly for 3

Guidelines for syphilis screening <sup>14-17</sup>		
Pregnant women	<ul> <li>Initial prenatal visit</li> <li>Early in the third trimester and at delivery for high-risk women</li> </ul>	
MSM	<ul> <li>Annually</li> <li>Every 3 to 6 months for high-risk men</li> </ul>	
Individuals with HIV	<ul><li>Annually</li><li>More frequent screening as needed</li></ul>	

consecutive weeks.<sup>16</sup> The dose may be split and given at two discrete injection sites.<sup>19</sup> For nonpregnant patients with penicillin allergy, the first-line recommended therapy is oral doxycycline 100 mg twice daily for 14 days for primary, secondary, and early latent disease, and 28 days for late latent syphilis.<sup>16</sup> Neurosyphilis requires a more complex regimen involving aqueous crystalline penicillin G administered I.V., potentially followed by benzathine penicillin I.M.<sup>16</sup> Treatment will not repair the injury to the central nervous system (CNS), but it may prevent further damage.<sup>9,16</sup> Some manifestations of tertiary syphilis should be managed in consultation with an infectious disease specialist.<sup>16</sup>

#### Syphilis during pregnancy

All women should be screened serologically for syphilis early in pregnancy. Pregnant women who test positive should be considered infected unless an adequate treatment history is documented and serologic antibody titers have declined appropriately for the stage of syphilis. The risk of antepartum fetal infection or congenital syphilis at delivery is related to the stage of syphilis during pregnancy, with the highest risk occurring in the primary and secondary stages.<sup>4</sup>

Pregnant women should receive the recommended penicillin treatment according to their stage of syphilis. Some specialists recommend women receive two doses of penicillin.<sup>11,16</sup> More than 40% of women treated for syphilis during pregnancy experience a Jarisch-Herxheimer reaction involving contractions, fetal distress, and even pregnancy loss. Thus, the first dose of penicillin G should be administered while supervised in an obstetric unit with continuous fetal monitoring for at least 24 hours.<sup>11</sup> After treatment, monthly titer checks are also recommended to ensure they are not increasing substantially because the risk of reinfection must be considered.<sup>11</sup>

Pregnant patients with penicillin allergy should undergo skin testing for penicillin allergy. If the skin test is

#### Syphilis stages and treatment<sup>16</sup>

Stages	Signs and symptoms	Treatment*
Primary	A single—or possibly more than one–round, firm, usually painless chancre lasting 3 to 6 weeks with or without treatment	Benzathine penicillin G, 2.4 million units I.M. in a single dose
Secondary	Nonitchy, rough, red or brownish skin rash. Possible sores in the mouth, vagina, or anus; large wartlike lesions in the mouth, axilla, or groin. Fever, lymphadenopathy, pharyngitis, headache, malaise, fatigue, and weight loss may occur.	Benzathine penicillin G, 2.4 million units I.M. in a single dose
Early latent	No physical signs of disease	Benzathine penicillin G, 2.4 million units I.M. in a single dose
Late latent or syphilis of unknown duration	No physical signs of disease	Benzathine penicillin G, 2.4 million units I.M. weekly for 3 consecutive weeks
Tertiary	Most people do not develop tertiary disease, which can affect the heart, brain, and nervous system and may cause death.	Managed in consultation with an infec- tious disease specialist. Testing for HIV infection and CSF examination should be performed before therapy is initiated.
Neurosyphilis	A wide range of symptoms are possible and can include headaches, altered muscle movements, paralysis, sensory impairment, and dementia. May occur at any stage of the disease.	Aqueous crystalline penicillin G, 18-24 million units per day, administered as 3-4 million units I.V. every 4 hours, or by continuous infusion for 10 to 14 days. Treatment will not repair injury to the CNS but may prevent further injury.

positive, penicillin desensitization is recommended, after which the first dose of penicillin can be administered with supervision and the ability to respond quickly to an acute reaction.<sup>11</sup> Patients referred for penicillin desensitization should be managed by an experienced obstetrician/gynecologist and/or a specialist in the field of allergy and immunology.<sup>11</sup> Congenital syphilis treatment should be managed by an obstetric specialist or neonatologist.<sup>11</sup> All cases must be reported to local health departments.

## Postexposure prophylaxis

PEP is another potential intervention for syphilis. In an open-label randomized trial, Molina et al. compared a group of high-risk MSM given doxycycline within 24 hours of sex to a control group that did not receive doxycycline.<sup>20</sup> They observed a relative risk reduction of 47% of a new bacterial STI in the treatment group and a 73% relative reduction of syphilis alone. Using doxycycline for PEP may be potentially useful; however, there is a risk for antibiotic resistance.<sup>20</sup>

## Population inequities

In 2019, 30.6% of all cases of chlamydia, gonorrhea, and primary and secondary syphilis were among

non-Hispanic Black Americans, even though they made up only approximately 12.5% of the US population. MSM are disproportionally impacted by STIs, including primary and secondary syphilis and gonorrhea.<sup>21</sup>

## **Conclusion**

The rate of primary and secondary syphilis in the US has increased almost every year since 2001 and have increased for both males and females since 2015. The syphilis rate for females more than doubled between 2014 and 2018 (172.7%). From 2017 to 2018, the rate increased 30.4%. Reported cases of congenital syphilis have increased in the last 6 years.<sup>4</sup> It is vital that NPs continue to screen for and treat confirmed cases of syphilis. Early prenatal care and early testing with each pregnancy will help to identify and successfully treat/ prevent congenital syphilis.

Mr. Carlo thanked the NP for spending time with him and explaining his risks of contracting HIV. He agreed that he is an excellent candidate for PrEP and was willing to start the medication. He also said he would try to be more consistent with condom use. Mr. Carlo returned to the clinic for his follow-up appointment a month later. He was feeling better and able to work without difficulty again.

He no longer needed over-the-counter pain relievers and, since his last visit, he had only used marijuana recreationally as opposed to needing it for sleep. He was taking his PrEP appropriately and both sexual partners were tested. Both were infected with syphilis as well and treated accordingly. They were using condoms more consistently but not at all times. He agreed to repeat his NTT titer at his 6- and 12-month visits. Follow-up care was arranged for all three patients and the NP continued to partner with the patients to improve their sexual health and safety.

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DOI-10.1097/01.NPR.0000790496.90015.74

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