

= Syphilis =

Syphilis is a sexually transmitted infection caused by the bacterium *Treponema pallidum* subspecies *pallidum*. The signs and symptoms of syphilis vary depending in which of the four stages it presents (primary , secondary , latent , and tertiary). The primary stage classically presents with a single chancre (a firm , painless , non @-@ itchy skin ulceration) but there may be multiple sores . In secondary syphilis a diffuse rash which frequently involves the palms of the hands and soles of the feet occurs . There may also be sores in the mouth or vagina . In latent syphilis there are little to no symptoms which can last for years . In tertiary syphilis there are gummas (soft non @-@ cancerous growths) , neurological , or heart symptoms . Syphilis has been known as " the great imitator " as it may cause symptoms similar to many other diseases .

Syphilis is most commonly spread through sexual activity . It may also be transmitted from mother to baby during pregnancy or at birth , resulting in congenital syphilis . Other human diseases caused by related *Treponema pallidum* include yaws (subspecies *pertenue*) , pinta (subspecies *carateum*) , and bejel (subspecies *endemicum*) . Diagnosis is usually made by using blood tests ; the bacteria can also be detected using dark field microscopy . The Center for Disease Control recommends all pregnant women be tested .

The risk of syphilis can be decreased by latex condom use or not having sex . Syphilis can be effectively treated with antibiotics . The preferred antibiotic for most cases is benzathine penicillin G injected into a muscle . In those who have a severe penicillin allergy , doxycycline or tetracycline may be used . In those with neurosyphilis intravenous penicillin G potassium or ceftriaxone is recommended . During treatment people may develop fever , headache , and muscle pains , a reaction known as Jarisch @-@ Herxheimer .

In 2013 syphilis infected about 315 @,@ 000 people . During 2010 it caused about 113 @,@ 000 deaths down from 202 @,@ 000 in 1990 . After decreasing dramatically with the availability of penicillin in the 1940s , rates of infection have increased since the turn of the millennium in many countries , often in combination with human immunodeficiency virus (HIV) . This is believed to be partly due to increased promiscuity , prostitution , decreasing use of condoms , and unsafe sexual practices among men who have sex with men . In 2015 , Cuba became the first country in the world to eliminate mother @-@ to @-@ child transmission of syphilis .

= = Signs and symptoms = =

Syphilis can present in one of four different stages : primary , secondary , latent , and tertiary , and may also occur congenitally . It was referred to as " the great imitator " by Sir William Osler due to its varied presentations .

= = = Primary = = =

Primary syphilis is typically acquired by direct sexual contact with the infectious lesions of another person . Approximately 3 to 90 days after the initial exposure (average 21 days) a skin lesion , called a chancre , appears at the point of contact . This is classically (40 % of the time) a single , firm , painless , non @-@ itchy skin ulceration with a clean base and sharp borders between 0 @.@ 3 and 3 @.@ 0 cm in size . The lesion may take on almost any form . In the classic form , it evolves from a macule to a papule and finally to an erosion or ulcer . Occasionally , multiple lesions may be present (~ 40 %) , with multiple lesions more common when coinfectd with HIV . Lesions may be painful or tender (30 %) , and they may occur outside of the genitals (2 ? 7 %) . The most common location in women is the cervix (44 %) , the penis in heterosexual men (99 %) , and anally and rectally relatively commonly in men who have sex with men (34 %) . Lymph node enlargement frequently (80 %) occurs around the area of infection , occurring seven to 10 days after chancre formation . The lesion may persist for three to six weeks without treatment .

= = = Secondary = = =

Secondary syphilis occurs approximately four to ten weeks after the primary infection . While secondary disease is known for the many different ways it can manifest , symptoms most commonly involve the skin , mucous membranes , and lymph nodes . There may be a symmetrical , reddish @-@ pink , non @-@ itchy rash on the trunk and extremities , including the palms and soles . The rash may become maculopapular or pustular . It may form flat , broad , whitish , wart @-@ like lesions known as condyloma latum on mucous membranes . All of these lesions harbor bacteria and are infectious . Other symptoms may include fever , sore throat , malaise , weight loss , hair loss , and headache . Rare manifestations include liver inflammation , kidney disease , joint inflammation , periostitis , inflammation of the optic nerve , uveitis , and interstitial keratitis . The acute symptoms usually resolve after three to six weeks ; about 25 % of people may present with a recurrence of secondary symptoms . Many people who present with secondary syphilis (40 ? 85 % of women , 20 ? 65 % of men) do not report previously having had the classic chancre of primary syphilis .

== Latent ==

Latent syphilis is defined as having serologic proof of infection without symptoms of disease . It is further described as either early (less than 1 year after secondary syphilis) or late (more than 1 year after secondary syphilis) in the United States . The United Kingdom uses a cut @-@ off of two years for early and late latent syphilis . Early latent syphilis may have a relapse of symptoms . Late latent syphilis is asymptomatic , and not as contagious as early latent syphilis .

== Tertiary ==

Tertiary syphilis may occur approximately 3 to 15 years after the initial infection , and may be divided into three different forms : gummatous syphilis (15 %) , late neurosyphilis (6 @.@ 5 %) , and cardiovascular syphilis (10 %) . Without treatment , a third of infected people develop tertiary disease . People with tertiary syphilis are not infectious .

Gummatous syphilis or late benign syphilis usually occurs 1 to 46 years after the initial infection , with an average of 15 years . This stage is characterized by the formation of chronic gummas , which are soft , tumor @-@ like balls of inflammation which may vary considerably in size . They typically affect the skin , bone , and liver , but can occur anywhere .

Neurosyphilis refers to an infection involving the central nervous system . It may occur early , being either asymptomatic or in the form of syphilitic meningitis , or late as meningovascular syphilis , general paresis , or tabes dorsalis , which is associated with poor balance and lightning pains in the lower extremities . Late neurosyphilis typically occurs 4 to 25 years after the initial infection . Meningovascular syphilis typically presents with apathy and seizure , and general paresis with dementia and tabes dorsalis . Also , there may be Argyll Robertson pupils , which are bilateral small pupils that constrict when the person focuses on near objects but do not constrict when exposed to bright light .

Cardiovascular syphilis usually occurs 10 ? 30 years after the initial infection . The most common complication is syphilitic aortitis , which may result in aneurysm formation .

== Congenital ==

Congenital syphilis is that which is transmitted during pregnancy or during birth . Two @-@ thirds of syphilitic infants are born without symptoms . Common symptoms that develop over the first couple of years of life include enlargement of the liver and spleen (70 %) , rash (70 %) , fever (40 %) , neurosyphilis (20 %) , and lung inflammation (20 %) . If untreated , late congenital syphilis may occur in 40 % , including saddle nose deformation , Higoumenakis sign , saber shin , or Clutton 's joints among others .

== Cause ==

== Bacteriology ==

Treponema pallidum subspecies *pallidum* is a spiral @-@ shaped , Gram @-@ negative , highly mobile bacterium . Three other human diseases are caused by related *Treponema pallidum* , including yaws (subspecies *pertenue*) , pinta (subspecies *carateum*) and bejel (subspecies *endemicum*) . Unlike subtype *pallidum* , they do not cause neurological disease . Humans are the only known natural reservoir for subspecies *pallidum* . It is unable to survive without a host for more than a few days . This is due to its small genome (1 @.@ 14 MDa) failing to encode the metabolic pathways necessary to make most of its macronutrients . It has a slow doubling time of greater than 30 hours .

== Transmission ==

Syphilis is transmitted primarily by sexual contact or during pregnancy from a mother to her fetus ; the spirochete is able to pass through intact mucous membranes or compromised skin . It is thus transmissible by kissing near a lesion , as well as oral , vaginal , and anal sex . Approximately 30 to 60 % of those exposed to primary or secondary syphilis will get the disease . Its infectivity is exemplified by the fact that an individual inoculated with only 57 organisms has a 50 % chance of being infected . Most (60 %) of new cases in the United States occur in men who have sex with men . It can be transmitted by blood products . It is tested for in many countries and thus the risk is low . The risk of transmission from sharing needles appears limited .

It is not generally possible to contract syphilis through toilet seats , daily activities , hot tubs , or sharing eating utensils or clothing . This is mainly because the bacteria die very quickly outside of the body , making transmission by objects extremely difficult .

== Diagnosis ==

Syphilis is difficult to diagnose clinically early in its presentation . Confirmation is either via blood tests or direct visual inspection using microscopy . Blood tests are more commonly used , as they are easier to perform . Diagnostic tests are unable to distinguish between the stages of the disease .

== Blood tests ==

Blood tests are divided into nontreponemal and treponemal tests . Nontreponemal tests are used initially , and include venereal disease research laboratory (VDRL) and rapid plasma reagin tests . As these tests are occasionally false positives , confirmation is required with a treponemal test , such as treponemal pallidum particle agglutination (TPHA) or fluorescent treponemal antibody absorption test (FTA @-@ Abs) . False positives on the nontreponemal tests can occur with some viral infections such as varicella (chickenpox) and measles , as well as with lymphoma , tuberculosis , malaria , endocarditis , connective tissue disease , and pregnancy . Treponemal antibody tests usually become positive two to five weeks after the initial infection . Neurosyphilis is diagnosed by finding high numbers of leukocytes (predominately lymphocytes) and high protein levels in the cerebrospinal fluid in the setting of a known syphilis infection .

== Direct testing ==

Dark ground microscopy of serous fluid from a chancre may be used to make an immediate diagnosis . Hospitals do not always have equipment or experienced staff members , whereas testing must be done within 10 minutes of acquiring the sample . Sensitivity has been reported to be nearly 80 % , thus can only be used to confirm a diagnosis but not rule one out . Two other tests can be

carried out on a sample from the chancre : direct fluorescent antibody testing and nucleic acid amplification tests . Direct fluorescent testing uses antibodies tagged with fluorescein , which attach to specific syphilis proteins , while nucleic acid amplification uses techniques , such as the polymerase chain reaction , to detect the presence of specific syphilis genes . These tests are not as time @-@ sensitive , as they do not require living bacteria to make the diagnosis .

= = Prevention = =

= = = Vaccine = = =

As of 2010 , there is no vaccine effective for prevention . Several vaccines based on treponemal proteins reduce lesion development in an animal model , and research is ongoing .

= = = Sex = = =

Abstinence from intimate physical contact with an infected person is effective at reducing the transmission of syphilis , as is the proper use of a latex condom . Condom use does not completely eliminate the risk . Thus , the Centers for Disease Control and Prevention recommends a long @-@ term , mutually monogamous relationship with an uninfected partner and the avoidance of substances such as alcohol and other drugs that increase risky sexual behavior .

= = = Congenital disease = = =

Congenital syphilis in the newborn can be prevented by screening mothers during early pregnancy and treating those who are infected . The United States Preventive Services Task Force (USPSTF) strongly recommends universal screening of all pregnant women , while the World Health Organization recommends all women be tested at their first antenatal visit and again in the third trimester . If they are positive , they recommend their partners also be treated . Congenital syphilis is still common in the developing world , as many women do not receive antenatal care at all , and the antenatal care others receive does not include screening , and it still occasionally occurs in the developed world , as those most likely to acquire syphilis (through drug use , etc .) are least likely to receive care during pregnancy . Several measures to increase access to testing appear effective at reducing rates of congenital syphilis in low- to middle @-@ income countries . Point @-@ of @-@ care testing to detect syphilis appeared to be good although more research is needed to assess its effectiveness and into improving outcomes in mothers and babies .

= = = Screening = = =

The CDC recommends that sexually active men who have sex with men be tested at least yearly . The USPSTF also recommends screening among those at high risk .

Syphilis is a notifiable disease in many countries , including Canada the European Union , and the United States . This means health care providers are required to notify public health authorities , which will then ideally provide partner notification to the person 's partners . Physicians may also encourage patients to send their partners to seek care . Several strategies have been found to improve follow @-@ up for STI testing including email and text messaging as reminders of appointments .

= = Treatment = =

= = = Early infections = = =

The first @-@ choice treatment for uncomplicated syphilis remains a single dose of intramuscular benzathine penicillin G. Doxycycline and tetracycline are alternative choices for those allergic to penicillin ; due to the risk of birth defects these are not recommended for pregnant women . Resistance to macrolides , rifampin , and clindamycin is often present . Ceftriaxone , a third @-@ generation cephalosporin antibiotic , may be as effective as penicillin @-@ based treatment . It is recommended that a treated person avoid sex until the sores are healed .

= = = Late infections = = =

For neurosyphilis , due to the poor penetration of penicillin G into the central nervous system , those affected are recommended to be given large doses of intravenous penicillin for a minimum of 10 days . If a person is allergic , ceftriaxone may be used or penicillin desensitization attempted . Other late presentations may be treated with once @-@ weekly intramuscular penicillin G for three weeks . If allergic , as in the case of early disease , doxycycline or tetracycline may be used , albeit for a longer duration . Treatment at this stage limits further progression but has only slight effect on damage which has already occurred .

= = = Jarisch @-@ Herxheimer reaction = = =

One of the potential side effects of treatment is the Jarisch @-@ Herxheimer reaction . It frequently starts within one hour and lasts for 24 hours , with symptoms of fever , muscle pains , headache , and a fast heart rate . It is caused by cytokines released by the immune system in response to lipoproteins released from rupturing syphilis bacteria .

= = = Pregnancy = = =

Penicillin is an effective treatment for syphilis in pregnancy but there is no agreement on which dose or way of giving it is most effective . More research is needed into how much antibiotic to give and when to give it .

= = Epidemiology = =

In 2013 syphilis infected about 315 @,@ 000 people . Syphilis is believed to have infected 12 million additional people in 1999 , with greater than 90 % of cases in the developing world . It affects between 700 @,@ 000 and 1 @.@ 6 million pregnancies a year , resulting in spontaneous abortions , stillbirths , and congenital syphilis . During 2010 it caused about 113 @,@ 000 deaths down from 202 @,@ 000 in 1990 . In sub @-@ Saharan Africa , syphilis contributes to approximately 20 % of perinatal deaths . Rates are proportionally higher among intravenous drug users , those who are infected with HIV , and men who have sex with men . In the United States , rates of syphilis as of 2007 were six times greater in men than women ; they were nearly equal in 1997 . African Americans accounted for almost half of all cases in 2010 . As of 2014 , syphilis infections continue to increase in the United States .

Syphilis was very common in Europe during the 18th and 19th centuries . Flaubert found it universal among nineteenth @-@ century Egyptian prostitutes . In the developed world during the early 20th century , infections declined rapidly with the widespread use of antibiotics , until the 1980s and 1990s . Since 2000 , rates of syphilis have been increasing in the USA , Canada , the UK , Australia and Europe , primarily among men who have sex with men . Rates of syphilis among American women have remained stable during this time , and rates among UK women have increased , but at a rate less than that of men . Increased rates among heterosexuals have occurred in China and Russia since the 1990s . This has been attributed to unsafe sexual practices , such as sexual promiscuity , prostitution , and decreasing use of barrier protection .

Untreated , it has a mortality of 8 % to 58 % , with a greater death rate in males . The symptoms of syphilis have become less severe over the 19th and 20th centuries , in part due to widespread

availability of effective treatment and partly due to decreasing virulence of the spirochaete . With early treatment , few complications result . Syphilis increases the risk of HIV transmission by two to five times , and coinfection is common (30 ? 60 % in some urban centers) . In 2015 Cuba became the first country in the world to eradicate mother to child transmission of syphilis .

= = History = =

The exact origin of syphilis is disputed . Syphilis was indisputably present in the Americas before European contact . The dispute is over whether or not syphilis was also present elsewhere in the world at that time . One of the two primary hypotheses proposes that syphilis was carried from the Americas to Europe by the returning crewmen from Christopher Columbus 's voyage to the Americas . The other hypothesis says that syphilis existed in Europe previously , but went unrecognized until shortly after Columbus ' return . These are referred to as the Columbian and pre @-@ Columbian hypotheses , respectively . The Columbian hypothesis is best supported by the available evidence . The first written records of an outbreak of syphilis in Europe occurred in 1494 or 1495 in Naples , Italy , during a French invasion (Italian War of 1494 ? 98) . As it was claimed to have been spread by French troops , it was initially known as the " French disease " by the people of Naples . In 1530 , the pastoral name " syphilis " (the name of a character) was first used by the Italian physician and poet Girolamo Fracastoro as the title of his Latin poem in dactylic hexameter describing the ravages of the disease in Italy . It was also known historically as the " Great Pox " .

The causative organism , *Treponema pallidum* , was first identified by Fritz Schaudinn and Erich Hoffmann in 1905 . The first effective treatment (Salvarsan) was developed in 1910 by Paul Ehrlich , which was followed by trials of penicillin and confirmation of its effectiveness in 1943 . Before the discovery and use of antibiotics in the mid @-@ twentieth century , mercury and isolation were commonly used , with treatments often worse than the disease .

Many famous historical figures , including Franz Schubert , Arthur Schopenhauer , and Édouard Manet , are believed to have had the disease . Friedrich Nietzsche was long believed to have gone mad as a result of tertiary syphilis , but that diagnosis has recently come into question .

= = = Arts and literature = = =

The earliest known depiction of an individual with syphilis is Albrecht Dürer 's Syphilitic Man , a woodcut believed to represent a Landsknecht , a Northern European mercenary . The myth of the femme fatale or " poison women " of the 19th century is believed to be partly derived from the devastation of syphilis , with classic examples in literature including John Keats ' *La Belle Dame sans Merci* .

The artist Jan van der Straet painted a scene of a wealthy man receiving treatment for syphilis with the tropical wood guaiacum sometime around 1580 . The title of the work is " Preparation and Use of Guayaco for Treating Syphilis " . That the artist chose to include this image in a series of works celebrating the New World indicates how important a treatment , however ineffective , for syphilis was to the European elite at that time . The richly colored and detailed work depicts four servants preparing the concoction while a physician looks on , hiding something behind his back while the hapless patient drinks .

= = = Tuskegee and Guatemala studies = = =

One of the most infamous United States cases of questionable medical ethics in the 20th century was the Tuskegee syphilis study . The study took place in Tuskegee , Alabama , and was supported by the U.S. Public Health Service (PHS) in partnership with the Tuskegee Institute . The study began in 1932 , when syphilis was a widespread problem and there was no safe and effective treatment . The study was designed to measure the progression of untreated syphilis . By 1947 , penicillin had been shown to be an effective cure for early syphilis and was becoming widely used to treat the disease . Its use in later syphilis was still unclear . Study directors continued the study and

did not offer the participants treatment with penicillin . This is debated , and some have found that penicillin was given to many of the subjects .

In the 1960s , Peter Buxtun sent a letter to the CDC , who controlled the study , expressing concern about the ethics of letting hundreds of black men die of a disease that could be cured . The CDC asserted that it needed to continue the study until all of the men had died . In 1972 , Buxtun went to the mainstream press , causing a public outcry . As a result , the program was terminated , a lawsuit brought those affected nine million dollars , and Congress created a commission empowered to write regulations to deter such abuses from occurring in the future .

On 16 May 1997 , thanks to the efforts of the Tuskegee Syphilis Study Legacy Committee formed in 1994 , survivors of the study were invited to the White House to be present when President Bill Clinton apologized on behalf of the United States government for the study .

Syphilis experiments were also carried out in Guatemala from 1946 to 1948 . They were United States @-@ sponsored human experiments , conducted during the government of Juan José Arévalo with the cooperation of some Guatemalan health ministries and officials . Doctors infected soldiers , prisoners , and mental patients with syphilis and other sexually transmitted diseases , without the informed consent of the subjects , and then treated them with antibiotics . In October 2010 , the U.S. formally apologized to Guatemala for conducting these experiments .