Infectious syphilis in high-income settings in the 21st century

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In high-income countries after World War II, the widespread availability of effective antimicrobial therapy, combined with expanded screening, diagnosis, and treatment programmes, resulted in a substantial decline in the incidence of syphilis. However, by the turn of the 21st century, outbreaks of syphilis began to occur in different subpopulations, especially in communities of men who have sex with men. The reasons for these outbreaks include changing sexual and social norms, interactions with increasingly prevalent HIV infection, substance abuse, global travel and migration, and underinvestment in public-health services. Recently, it has been suggested that these outbreaks could be the result of an interaction of the pathogen with natural immunity, and that syphilis epidemics should be expected to intrinsically cycle. We discuss this hypothesis by examining long-term data sets of syphilis. Today, syphilis in western Europe and the USA is characterised by low-level endemicity with concentration among population subgroups with high rates of partner change, poor access to health services, social marginalisation, or low socioeconomic status.

Introduction

Syphilis remains a global problem, with an estimated 12 million people infected every year.[1] Congenital syphilis, a consequence of infection during pregnancy, results in serious adverse outcomes in up to 80% of cases and is estimated to affect over 1 million pregnancies annually,[2–4] despite the existence of simple, validated screening tests, effective prevention measures, and cheap treatment options. In many high-income countries, successes in syphilis prevention and control were accelerated during the early and mid-1990s, with many countries approaching or achieving elimination of endemic disease transmission.[5] However, since the beginning of the 21st century, syphilis incidence has started to rise in high-income settings, in part driven by increases in cases among men who have sex with men, although more recent increases among heterosexual people have also been reported.[6,7] We examine the recent epidemiology, prevention, and control of infectious syphilis in high-income settings, mainly focusing on western Europe and the USA. We also examine long-term data-sets of syphilis, and the results of published mathematical models of the natural history and transmission dynamics of this infection; we relate these to future opportunities for disease control.

Biology of syphilis

Syphilis, caused by the spirochaete *Treponema pallidum* subsp *pallidum*, belongs to a family of spiral-shaped bacteria, the Spirochaetaceae (spirochaetes), and is related to other pathogenic treponemes that cause non-venereal diseases: *T pallidum* subsp *endemicum* (bejel), *T pallidum* subsp *pertenue* (yaws), and *Treponema carateum* (pinta). The *T pallidum* subspecies are virtually identical based on their morphology, antigenic properties, and DNA homology, although more recent evidence suggests that there may be molecular signatures that can be used to differentiate the subspecies.[8,9] *T pallidum* subsp *pallidum* is an obligate human parasite, and there are no reservoirs for this organism in animals or in the environment. Most cases of venereal syphilis are acquired through direct sexual contact with lesions of an individual who has active primary or secondary syphilis, and transmission occurs in approximately half of such contacts.[10] Syphilis can be transmitted vertically from an infected mother to the fetus by transplacental passage of treponemes. Blood-borne, non-sexual personal contact and accidental direct inoculation are less common modes of transmission.

After inoculation and penetration of the mucosal surfaces or abraded skin, *T pallidum* subsp *pallidum* attaches to host cells and initiates multiplication.[10] A primary lesion develops at the site of inoculation 2–6 weeks after infection. It begins as a painless indurate papule whose surface necroses to form a hard-based, well circumscribed, ulcerated lesion (chancre) that is teeming with treponemes. Lesion resolution and clearance of treponemes are largely attributed to cell-mediated immune mechanisms involving phagocytosis by macrophages that have been activated by lymphokines released from antigen-specific sensitised T cells. However, despite the destruction of billions of treponemes by the host immune responses, some organisms survive to cause chronic infection.[10] LaFond and colleagues[11,12] have reported that the *tprK* gene of *T pallidum* undergoes antigenic variation in seven variable regions, which in turn elicit a variant-specific antibody response, thereby supporting the hypothesis that TprK variants may help organisms to avoid the developing immune response in infected individuals, contributing to the ability of *T pallidum* to establish chronic infection.[11]

Secondary syphilis results from the multiplication and dissemination of treponemes throughout the body. *T pallidum* subsp *pallidum* is found in many different tissues despite the presence of high concentrations of antitreponemal antibodies.[10] The secondary stage occurs up to 6 months after the healing of the primary lesion and is characterised by a wide range of clinical signs and symptoms including malaise, low grade fever, headache, rash, generalised lymphadenopathy, rash on the palms and soles of the feet, mucous patches in the oral cavity or genital tract, condylomata lata in moist intertriginous

regions, and alopecia. The secondary stage lasts for several weeks or months and may reoccur in approximately 25% of untreated patients.[10]

Secondary lesions usually subside within a few weeks,[10] but despite the absence of clinical symptoms, serological evidence confirms that organisms are still present—usually in the spleen and lymph nodes. This latent phase may be divided into early (the first year of infection) and late (beginning 1 year after infection) stages. Compared with secondary syphilis, late latent syphilis is associated with relative immunity to recurrence of active disease and increasing resistance to reinfection with the homologous treponemal strain. Latency can last for many years; approximately two-thirds of untreated patients with latent syphilis will remain in this stage for the remainder of their lives.[10] Spontaneous cures are thought to be unusual.

The tertiary or late stage of syphilis is rarely seen today in the era of effective and prevalent antibiotic therapy. In historical studies of the natural history of untreated syphilis, tertiary syphilis occurred in a third of untreated patients, usually 20–40 years after the onset of infection.[10,13] Treponemes invade the CNS, cardiovascular system, eyes, skin, and other internal organs, producing damage as a result of their invasive properties and inflammation. Replication of treponemes in the wall of the aorta may lead to aneurysm, aortitis, or aortic endocarditis. Neurosyphilis may be symptomatic or asymptomatic and includes meningeal, meningovascular, and parenchymatous syphilis. Gumma—destructive lesions in the skin, bones, or viscera—may occur singly or multiply and vary in size from microscopic defects to large tumour-like masses. During the tertiary phase, transmission by sexual contact does not occur and vertical transmission rarely occurs.

With minor differences, syphilis generally presents similarly in HIV-infected and HIV-uninfected patients.[14] In primary syphilis, HIV-infected patients may present with more than one chancre (up to 70% of patients) and with larger and deeper lesions.[15,16] About a quarter of HIV-infected patients present with concomitant lesions of both primary and secondary stages of syphilis at the time of diagnosis.[15] Approximately one-third of patients with early syphilis have invasion of treponemes in the cerebrospinal fluid (CSF), regardless of their HIV status.[16] However, by contrast with HIV-uninfected patients, most of the new cases of clinical neurosyphilis in HIV-infected individuals are identified early at the initial presentation,[17] suggesting that HIV infection may be associated with an increased risk of developing neurological complications.[18]

History of syphilis

The first well-recorded outbreak of a venereal disease with the pathology of syphilis occurred in Naples, Italy, in 1494, 1 year after the return of Christopher Columbus from the New World. Through the remainder of the 15th century and the beginning of the 16th century, Europe experienced a rampant syphilis epidemic that reached

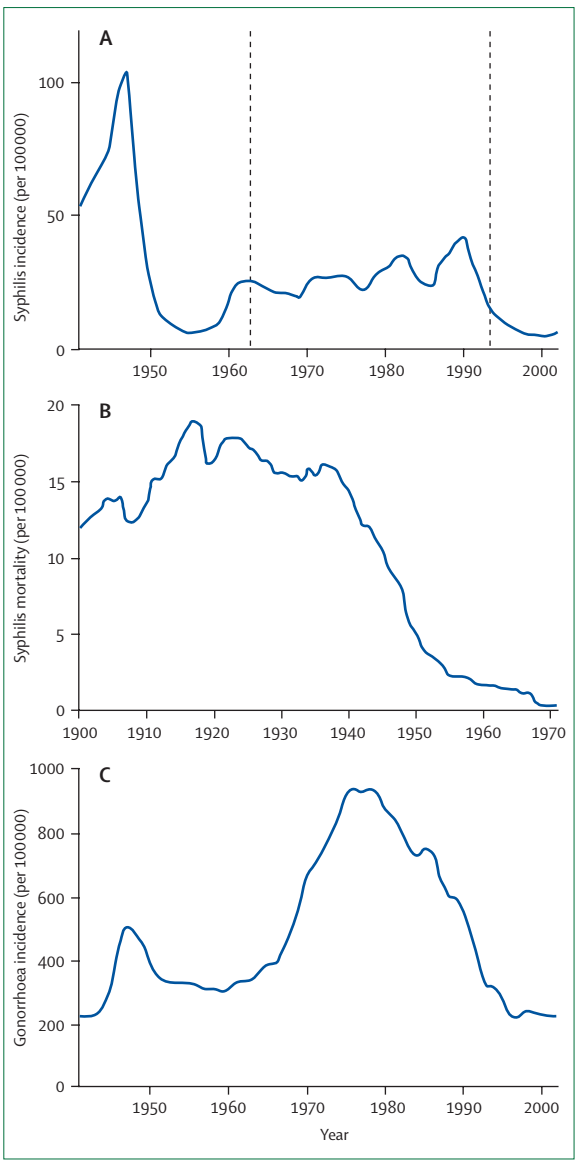

***Figure 1*: Temporal trends in syphilis and gonorrhoea in the USA**
(A) Syphilis incidence rates from 1941–2002. The dotted lines contain data from 1963–93. (B) Syphilis mortality rates from 1900–71. (C) Gonorrhoea incidence rates in the USA from 1941–2002.

Germany, Switzerland, England, and Holland. The epidemic also spread to India, China, and Japan. The 16th century syphilis epidemic was known as the great pox (to distinguish it from smallpox).[19]

Two major theories have been suggested to explain the invasion of syphilis in 15th century Europe.[19,20] The Columbian theory states that Columbus and his crew brought syphilis from the New World, since syphilis lesions have been found in pre-Columbian skeletons of Native Americans.[20] By contrast, the pre-Columbian theory states that syphilis was present in Europe long before Columbus, an argument supported by various 13–14th century references to venereal leprosy (which was also vertically

transmitted) and skeletal remains with treponemal lesions from European archaeological sites.[20] The question of the origin of syphilis is still awaiting resolution.[21,22]

During the colonial period, syphilis (and other infectious diseases) spread, with severe consequences, from European countries to the most isolated corners of the world.[23] A breakthrough was made on March 3, 1905, by Schauddin and Hoffmann, who discovered that a bacterium (now known as *T pallidum*) was the cause of syphilis.[24] However, the traditional and rather ineffective treatment with mercury remained common. Observational studies of untreated patients were done to better understand the clinical evolution of the disease.[13,25] Perhaps the most infamous of these was the 1932 Tuskegee study of untreated syphilis, a study of the natural history of syphilis in 600 black men (399 with syphilis, 201 without syphilis) in the hope of justifying treatment programmes for black people. The study was done without the benefit of patients' informed consent. Researchers told the men they were being treated for "bad blood", a local term used to describe several ailments, including syphilis, anaemia, and fatigue, but in reality, the participants did not receive the proper treatment needed to cure their illness. In exchange for taking part in the study, the men received free medical examinations, free meals, and burial insurance. Although originally designed to last 6 months, the study actually went on for 40 years. The ethical systems put in place after the outcry over Tuskegee helped promote changes in the regulations that now govern research among human beings.[26]

In 1928, Fleming discovered penicillin which, in 1943, was first introduced as a treatment for syphilis, with substantial improvements in prognosis.[24] In the USA, the incidence of syphilis during World War II was over 500 000 infections per year (figure 1). Between 1945 and 2000, syphilis incidence declined in several stages to 31 575 reported infections per year. Incidence first declined steeply (after the introduction of penicillin in the 1940s[27]), then stabilised at an approximate endemic level for several decades. More recently, incidence declined to a low level that has been sustained by outbreaks (figure 1). Similar patterns in disease incidence were observed in many European countries.[6,7] Although rates and numbers of reported syphilis cases in the USA and western Europe approached their lowest levels during the mid-1990s, disease outbreaks have recently been reported along the bicoastal areas of the USA, and in western Europe and the UK.[5,7]

Current epidemiology of syphilis

Syphilis is distributed worldwide, but it is particularly problematic in developing countries, where the disease is a leading cause of genital ulcers. Globally, most cases occur in sub-Saharan Africa and southeast Asia.[1] In these settings, the predominant mode of transmission is through heterosexual intercourse, although vertical transmission of infection remains a major concern. Seroprevalence studies from the 1970s and 1980s reviewed by Hira and colleagues[28] showed a wide range of seroprevalence values among pregnant women, from 0·03% in Scotland to 16·0% in Brazil. However, comparing prevalence and incidence data across countries is difficult because of differences in surveillance systems, case definitions, and reporting requirements.[29]

Numbers and rates of infectious syphilis fell to their lowest levels in many European Union (EU) countries by the early 1990s,[30,31] despite substantial increases in syphilis incidence in Russia.[32,33] The decreases in western Europe were accompanied by marked reductions in the incidence of congenital syphilis and tertiary disease. By 1995, with the exception of Germany, fewer than 300 cases of infectious syphilis were recorded in any of the reporting EU countries.[34] Among these cases, endemic transmission was rare, with most infections being diagnosed among migrants from high-prevalence countries or among EU nationals who had sexual contact with infected individuals outside the region.

Since 1996, syphilis has again been on the increase in many northern and western EU countries.[34] In Denmark, diagnoses of infectious syphilis increased by more than 50% between 1999 and 2002,[35] and in Belgium, between 2000 and 2002, a 3·5-fold increase in the number of laboratory-diagnosed syphilis cases was detected by sentinel networks of laboratories.[36] In Austria, the notified number of syphilis cases steadily increased from 124 in 1993 to 420 in 2002, with about 70% of cases reported in Vienna. Other major urban centres such as London, Dublin, Berlin, Paris, and Rotterdam all showed huge increases in syphilis reports during this period, predominantly among populations of men who have sex with men.[37–40] Increases in the UK were initially observed in larger cities and then progressed to suburban and rural settings.[41]

In the late 1980s and early 1990s, syphilis re-emerged in the USA and became focused in urban and rural southern regions and in large urban centres throughout the country.[5] The demographics of the disease changed from an infection affecting predominantly white men who have sex with men to one affecting mainly heterosexual African-Americans.[42,43] As in other high-income settings, rates of primary and secondary syphilis reported in the USA decreased during the 1990s, and by early 2000, the rate was the lowest since reporting began in 1941 (figure 1).[5]

The resurgence of primary and secondary syphilis in the USA began in late 2000 and has continued unabated.[44] Overall, increases in syphilis rates during 2000–04 were observed only among men. In 2004, for the first time in over 10 years, the rate of primary and secondary syphilis among women did not decrease; it remained the same between 2003 and 2004 at 0·8 cases per 100 000 population.[44] The southern USA accounted for 48% and 43% of primary and secondary syphilis cases in 2004 and 2003, respectively (see figure 2, webfigure 1 and

webfigure 2).[44] An increase in syphilis cases among men who have sex with men in the USA occurred between 2000 and 2005, characterised by high rates of HIV co-infection and high-risk sexual behaviour.[45–47]

Syphilis incidence in the USA shows tremendous variation across racial and ethnic groups. In 2004, the rate of primary and secondary syphilis reported among African-American people (9·0 cases per 100 000 population) was six times greater than the rate among non-Hispanic white people (1·6 cases per 100 000 population).[44] Congenital syphilis continues to decline in the USA; the overall rate in 2004 was 8·8 cases per 100 000 livebirths—a 92% decrease since 1991.[44] This decline reflects the substantial reduction in the rate of primary and secondary syphilis in women in the past decade.[44]

Syphilis increases have been reported in other developed countries including Canada, Australia, and New Zealand,[48–52] and although the magnitude of the increases and the affected populations vary, many of the driving factors are similar. Since syphilis facilitates both the transmission and the acquisition of HIV infection,[53,54] concomitant expansion in the HIV epidemic—especially among men who have sex with men in developed countries—has been a major concern. Studies from western Europe provide evidence of parallel increases in syphilis and HIV incidence;[55–57] however, studies from various US cities have not supported this trend.[58–60] Although the reasons for the discordance in trends are unknown, possible mechanisms include the high frequency of serosorting among men who have sex with men,[61–63] and the common practice of oral sex,[64] which differentially facilitates the spread of syphilis rather than HIV infection.

Determinants of syphilis transmission

As is the case with all sexually transmitted infections, the epidemic trajectories of syphilis are in fact composed of subtrajectories.[65,66] Consequently, the social determinants of syphilis epidemics are distinct according to the particular demographic, social, and behavioural subgroups in which they occur. For example, we can differentiate social determinants of syphilis epidemiology into three broad categories: (1) general populations of developing countries, (2) low socioeconomic status minority populations of developed countries, and (3) homosexual men.

In developed country settings, the social determinants of syphilis among low socioeconomic status minority subpopulations have perhaps been best studied in the USA. The remarkable resurgence of syphilis in the USA in the late 1980s and early 1990s, which affected minority populations disproportionately, resulted in in-depth explorations of the societal conditions associated with the spread of syphilis.[67,68] Unsurprisingly, similar drivers to those found in developing countries were observed, including poverty, youthful age composition, scarcity of men, low status of women, lower access to acceptable health services, and minority race and ethnic origin. The epidemiological impact of these social determinants is magnified by prevalent patterns of sexual mixing, particularly race/ethnicity-assortative sexual mixing.[69] Thus, the social context creates potential sex partner pools of individuals with high-risk sexual behaviours and high syphilis prevalence; this leads to a higher probability of exposure to infection for each sex act. During this heterosexual syphilis resurgence in the USA, risk of infection was further exacerbated by the epidemic of crack cocaine use.[70]

Currently, syphilis prevalence and incidence rates among poor subpopulations of ethnic minority in the USA are not

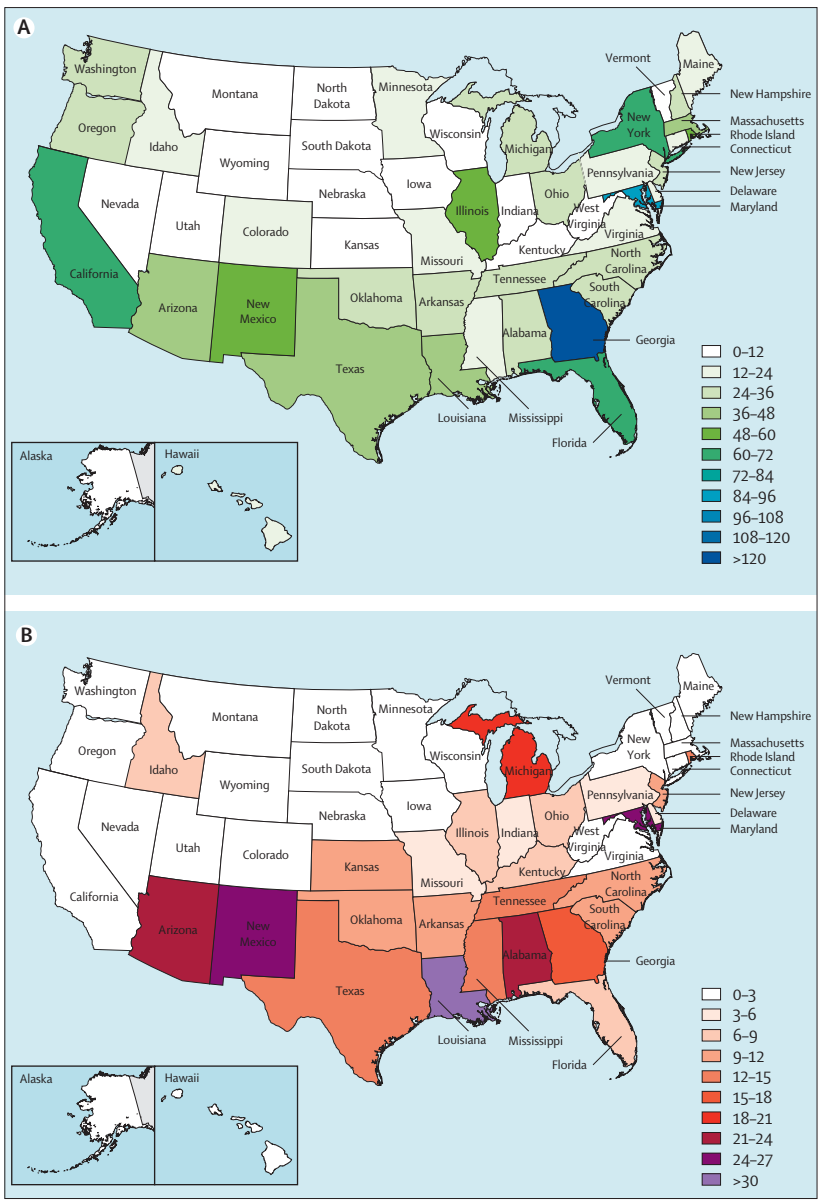

***Figure 2*: Primary and secondary syphilis incidence rates in the USA, 2003**
(A) Male population. (B) Female population. The colour scale on the right shows the incidence per 1 000 000 people. See webfigure 1 and webfigure 2 for animated US maps of syphilis cases versus time.

See Online for webfigure 1 and webfigure 2

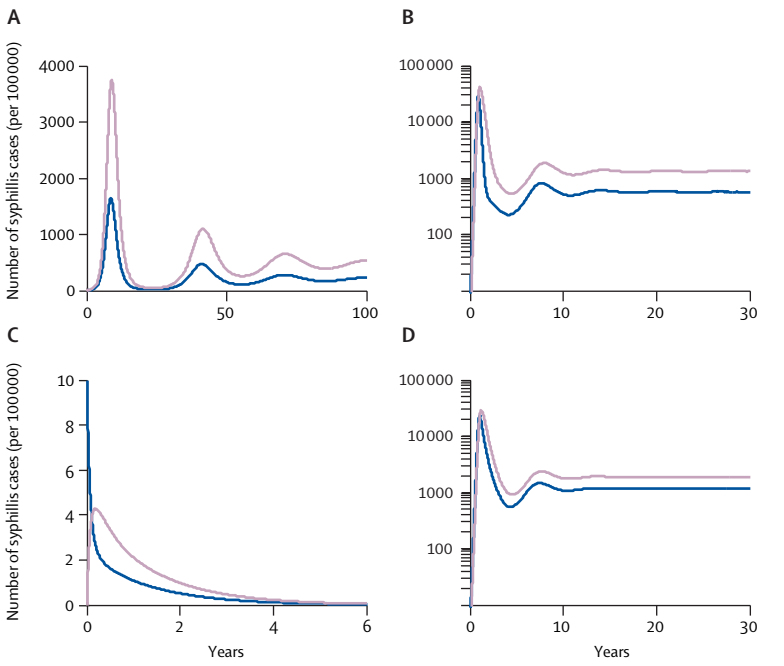

***Figure 3*: Dynamics of syphilis entering a susceptible population**
Incidence of primary (blue) and secondary (purple) syphilis are shown for (A) moderate rates of sexual partner exchange (c=5) when treatment is unavailable, (B) high rates of sexual partner change (c=40) with treatment unavailable, (C) moderate rates of sexual partner exchange (c=5) when 30% of cases are treated, and (D) high rates of sexual partner change (c=40) with 30% of cases treated. Based on the model of Garnett and colleagues.[88] c=average number of new sex partners per year for each individual in the population. Please note logarithmic scale in panels B and D.

high, compared with rates seen four or five decades ago. As mentioned previously, men who have sex with men have again become an important subpopulation in syphilis epidemiology,[6] with the use of sex enhancing and other recreational drugs—eg, the combined use of sildenafil and methamphetamines—promoting concurrent sexual partnerships, increased rates of new partner acquisition, and short intervals between new sex partners, all of which enhance sexual spread of infections. Bath houses (eg, saunas), circuit parties, and the internet—all part of contemporary social interactions for men who have sex with men—influence the nature of sexual mixing patterns, which in turn increase disease transmission risk.[71,72]

Modelling the transmission dynamics of syphilis

Mathematical models can provide insights into disease transmission dynamics.[73–77] The first models of syphilis epidemics were published in the 1980s.[78–81] More recently, Armstrong and colleagues[82] analysed infectious disease mortality records in the USA. Syphilis mortality was high early in the 20th century and remained at around 15 deaths per 100 000 population per year until 1943 when penicillin was introduced (figure 1). By 1950, syphilis mortality had decreased substantially, and in 1975 was 0·2 deaths per 100 000 population per year.[82]

Time-series modelling has been used to evaluate syphilis epidemics.[83,84] Grassly and colleagues[85] recently proposed a hypothesis that because of immunity, syphilis epidemics intrinsically cycle every 8–11 years. Their hypothesis is based on a spectral analysis of aggregated incidence data using 30 years (1960–93) of a Centers for Disease Control and Prevention (CDC) data set collected over a 60-year period (1941–2001; figure 1). However, when the entire 60-year data set was evaluated, no evidence was found that syphilis epidemics cycle.[86] Furthermore, detailed data analyses by the CDC show that data aggregation generates a misleading view of syphilis transmission dynamics.[86] Syphilis "epidemics" in 1982, 1990, and 2003 occurred in distinct subpopulations with extremely different sex, age, race, and geographical characteristics,[87] indicating that three independent outbreaks occurred rather than showing that syphilis epidemics intrinsically cycle. These outbreaks were likely the result of the HIV epidemic, changes in sexual behaviour (that were also reflected in gonorrhoea [figure 1]), and changes in intensity of control programmes.[87]

To assess syphilis dynamics, Garnett and colleagues[88] constructed a biologically realistic transmission model. They found that after the introduction of the first cases of syphilis the incidence stabilised, through damped oscillations, to an endemic level within 25–100 years (figure 3). Hence their results show that, since syphilis epidemics began hundreds of years ago, current incidence rates should not be expected to oscillate. They also determined that when treatment was introduced in the 1940s the transmission dynamics changed substantially. Incidence rates quickly and monotonically declined to a stable lower endemic level. Their predictions are in accord with the long-term CDC data sets (figure 1) and those by Breban and colleagues.[86]

Modelling has also been used to assess the impact of mass treatment interventions.[89,90] Oxman and colleagues[90] found that targeting high-risk groups could be very effective for syphilis control; and Pourbohloul and colleagues[89] determined that mass treatment should continue for several years after an outbreak appears to have been controlled. Outbreaks of syphilis are to be expected if risky sexual behaviour increases or treatment rates decrease, or both, as has happened over the past few decades.

Diagnosis, treatment, and control of syphilis

Diagnosis

Definitive laboratory diagnosis of early syphilis infection depends upon the use of darkfield microscopic examinations and direct fluorescent antibody tests of lesion exudate or tissue.[91,92] A presumptive diagnosis is possible through the use of two types of serological test for syphilis: (1) non-treponemal tests, which include the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests; and (2) treponemal tests, which detect antibody specific to *T pallidum*, and include enzyme immunoassay (EIA), *T pallidum* haemagglutination assay (TPHA), *T pallidum* particle agglutination test (TPPA), and fluorescent treponemal antibody with absorption test

(FTA-ABS).[93] EIAs can test for anti-IgG alone or IgG and IgM in combination. EIAs are being increasingly used as the initial screening test because of their high specificity, high sensitivity, and suitability for automation.[94] If the EIA is positive, diagnosis is confirmed with another treponemal test, usually the TPPA or TPHA. Both tests are very sensitive and specific, particularly the TPPA. A non-treponemal test is then undertaken to assist in diagnosing the stage of infection. For most HIV-infected patients, serological tests are accurate and reliable for the diagnosis of syphilis and for following the response to treatment, as in the general population.[92]

Non-treponemal tests should be repeated when used for diagnosis, because false-positive test results may occur secondary to various medical conditions.[92,94] Non-treponemal test antibody titres usually correlate with disease activity, and results should be reported quantitatively. A four-fold change in titre, equivalent to a change of two dilutions (eg, from 1/16 to 1/4, or from 1/8 to 1/32), is considered necessary to demonstrate a clinically significant difference between two non-treponemal test results that were obtained from the same serological test.[92] Sequential serological tests in individual patients should be done with the same testing method (eg, VDRL or RPR), preferably by the same laboratory.[92,94] The VDRL and RPR are equally valid assays, but quantitative results from the two tests cannot be compared directly because RPR titres are often slightly higher than VDRL titres.[92–94] Non-treponemal tests usually become non-reactive with time after treatment;[93,94] however, in some patients, non-treponemal antibodies can persist at a low titre for a long period of time, sometimes for the life of the patient (a serofast reaction).

Among the treponemal tests, EIAs that detect both IgG and IgM are recommended because they tend to be more sensitive in primary infection.[92–94] To improve sensitivity for early detection, the EIA IgM test should be done in addition to routine screening tests in all cases of genital ulceration as well as in patients who are known contacts of syphilis.[92,95] The TPPA is generally recommended in preference to the TPHA, and screening with either EIA alone or the TPPA alone is recommended.[92–94] The TPHA can be used in combination with non-treponemal tests (eg, VDRL or RPR) to maximise the detection of primary infection on screening.[92–94,96] Regarding confirmation of treponemal tests, a quantitative TPPA should be used to confirm a positive EIA, and an EIA should be used to confirm a positive TPPA.[92,94,97] Most patients who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of treatment or disease activity.[94] However, 15–25% of patients treated during the primary stage revert to being serologically non-reactive after 2–3 years.[92,94] In general, treponemal test antibody titres correlate poorly with disease activity and should not be used to assess treatment response.[94]

The diagnosis of neurosyphilis usually depends on various combinations of reactive serological test results, abnormalities of CSF cell count or protein, or a reactive VDRL-CSF with or without clinical manifestations.[92] The VDRL-CSF is the standard serological test, and when reactive in the absence of substantial contamination of CSF with blood, is deemed diagnostic of neurosyphilis. However, VDRL-CSF can be non-reactive when neurosyphilis is present. Therefore, some specialists recommend doing an FTA-ABS test on CSF, which is less specific for neurosyphilis than VDRL-CSF, but still highly sensitive. Some specialists believe that a negative CSF FTA-ABS test excludes neurosyphilis.

Although syphilis can be accurately diagnosed with serological tests in most patients, direct testing methods—such as darkfield microscopic examination, direct fluorescent antibody-*Treponema pallidum*, and PCR—should be considered when the diagnosis of syphilis cannot be confirmed.[14] More recent advances in syphilis diagnosis include the development of a multiplex PCR for the aetiological evaluation of genital ulcer disease. This technique has shown sensitivities of 100%, 98%, and 91% for the detection of herpes simplex virus, *Haemophilus ducreyi*, and *T pallidum*, respectively.[14,98] Other new technologies for diagnosing syphilis are currently under evaluation or early implementation. A non-treponemal test that uses the EIA format (SpiroTek Reagin II EIA; Organon Teknika, Durham, NC, USA) has recently been found to be more sensitive (93% *vs* 86%) and equally specific, compared with traditional RPR.[14,99] Several new treponemal tests (including rapid point-of-care tests) have shown excellent performance by using preparations of recombinant *T pallidum* antigens.[14,100,101]

Treatment

The efficacy of penicillin for the treatment of syphilis has been well established through over 50 years of clinical experience. Almost all treatment recommendations are based on expert opinions, which have been reinforced by case series and clinical trials.[92,102] Benzylpenicillin (penicillin G), administered parenterally, is the preferred drug for treatment of all stages of syphilis, including syphilis during pregnancy.[92] The preparations used (ie, benzathine, aqueous procaine, or aqueous crystalline), the dosage, and the length of treatment depend on the stage and clinical manifestations of disease and by geographical region. In the USA, benzathine benzylpenicillin (penicillin G benzathine) is the recommended preparation,[92] whereas the procaine salt of penicillin (600 000 IU intramuscularly for 10–14 days) is recommended or preferred in many European countries.[102,103] The Jarisch-Herxheimer reaction, an acute febrile reaction frequently accompanied by headache, myalgia, and other symptoms, usually occurs within the first 24 h after any therapy for syphilis, although most often among patients who have early syphilis infection. Patients should be informed about this possible adverse reaction.

Compared with HIV-negative patients, HIV-positive patients who have early syphilis may be at increased risk

for neurological complications and may have higher rates of treatment failure with currently recommended regimens.[14] Once the diagnosis of syphilis has been established, HIV-infected patients should be treated in accordance with the same recommendations as for HIV-uninfected patients.[92] In the USA, benzathine benzylpenicillin continues to be the drug of choice for all stages of syphilis in HIV-infected patients.[92] Careful follow-up after therapy is essential. Although there has been some debate on the theoretical benefit of prolonged exposure to therapeutic doses of penicillin, limited data suggest that there is no difference between standard and prolonged regimens.[104] Very limited data exist for the use of alternative treatment regimens in HIV-infected patients, such as doxycycline, tetracycline, and ceftriaxone, but there is likely to be few differences in outcome compared with HIV-negative patients.[105,106]

For patients who are allergic to penicillin, macrolides and cephalosporins can be used, with certain caveats.[92] Although azithromycin was thought of as a promising alternative oral agent for the treatment of early syphilis,[107] recent studies from the USA and Ireland have identified macrolide-resistant strains associated with a single base mutation in the 23S rRNA gene.[108–110] In cities with high rates of macrolide-resistant strains, penicillin should remain the drug of choice. In other cities, although certain situations may warrant the use of azithromycin to treat syphilis, it is imperative that the patient is monitored carefully with clinical re-evaluation and serological testing to ensure efficacy of treatment.

Public-health control

Strong case finding and robust disease surveillance are the cornerstone of an effective public-health response to syphilis epidemics.[92] Routine screening in antenatal populations and in high-risk populations, such as attendees at sexually transmitted disease clinics, have enabled effective targeting of resources and have limited vertical transmission in developed countries.[111,112] New rapid diagnostic tests and technologies that rely on oral fluid collection and testing will greatly facilitate testing of high-risk individuals in the community.[113] Social network methods that widen the net of peers and partners with similar high-risk lifestyles enhance and augment partner notification activities, and are all promising developments.[114]

Early diagnosis is essential both to link patients to effective care and to prevent the spread of infection. This is particularly the case in areas with outbreaks of syphilis, and among individuals who may, because of sexual behaviour or HIV status, have atypical disease presentations. Voluntary syphilis screening and linkage to care should become a normal part of medical practice in high-incidence areas or population subgroups, similar to screening for other treatable conditions, such as high cholesterol levels and breast cancer. Indeed, for some groups with hyperendemic levels of disease, routine periodic screening (at least annually among high-risk groups such as men who have sex with men) is strongly recommended.[92] HIV testing is crucial for all patients with a new diagnosis of syphilis.[92]

Partner notification remains an important tool for ensuring that close contacts of those newly diagnosed with syphilis are informed of their exposure risk and offered the opportunity for testing and care.[115–117] In the USA, the suggested periods for considering a contact as at-risk are 3 months plus duration of symptoms for primary syphilis; 6 months plus duration of symptoms for secondary syphilis; and 1 year for early latent syphilis.[92] Current CDC guidelines suggest that individuals who were exposed within the 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in a sex partner might be infected even if seronegative; therefore, such individuals should be treated presumptively.[92] For purposes of partner notification and presumptive treatment of exposed sex partners, patients with syphilis of unknown duration who have high non-treponemal serological test titres (ie, ≥1/32) are assumed to have early syphilis; however, the index case should be treated for latent syphilis if the CSF is normal.[92] Long-term sex partners of patients who have latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation findings.[92]

Marked variations in partner notification practice and standards for syphilis exist across Europe,[118,119] and have become more challenging within the context of the recent epidemics in men who have sex with men.[120] Although the notification of partners by public-health counsellors is more effective than notification by individual patients,[121] this approach is rarely used in most areas. Additionally, the policy of offering partner notification only at the time of syphilis diagnosis ignores the continuing high-risk sexual behaviour of many HIV-positive people.[122] New methods for partner notification, involving the adoption of more client-centred approaches and social network approaches may be particularly useful.[123–126] Combined with the use of newer antibody or nucleic acid-amplification tests,[9,14] these approaches could potentially stop clusters of transmission.

Other proven interventions, such as mass-media education campaigns, interventions to change high-risk behaviour in groups with a high prevalence of syphilis infection, distribution and use of condoms, expanded screening especially in outreach settings, and linkage to care, are all useful tools to prevent syphilis in community settings.[127,128] Involving affected communities in finding solutions to local outbreaks and epidemics has been a key strategy for enhancing syphilis prevention, and is a guiding principle of the US Syphilis Elimination Effort.[129] Community involvement and organisational coalitions between sexually transmitted disease programmes and community-based and service organisations, are crucial for intervention efforts that promote syphilis prevention in ethnic minorities.[130,131]

Search strategy and selection criteria

We searched Medline and Embase for articles published between Jan 1, 2000 and Jan 1, 2007. We used the search term "syphilis" and limited the search to "humans" and "English". We also reviewed commonly referenced and highly regarded older publications. Reference lists of articles identified by the search strategy were reviewed for relevant publications. Several review articles or book chapters were included because they provided comprehensive overviews.

Conclusions

In developed countries, the low incidence of syphilis over the past two decades and interactions of the disease with HIV infection, have resulted in clinicians who are unfamiliar with the disease's many manifestations. The recent resurgence among men who have sex with men and some high-risk heterosexual populations raises cause for concern, and demands renewed vigilance among, and training of, health-care professionals. Similarly, efforts must be made to incorporate and evaluate new diagnostic tools, social network approaches, innovative evidence-based prevention interventions, robust disease surveillance, and systematic monitoring and evaluation of prevention, treatment, and care activities.

Conflicts of interest

We declare that we have no conflicts of interest.

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