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Review

Syphilis transmission: a review of the current evidence

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Abstract. Syphilis remains widespread worldwide, with increasing rates among men who have sex with men. This paper reviews available evidence regarding syphilis transmission, including data on: sexual transmission (transmission probability per sexual partnership), vertical transmission, transmission via blood products and organ donation, and other rare modes of transmission. In addition, host susceptibility to syphilis infection is discussed. Syphilis screening and treatment, condoms and risk-reduction counselling and how they modify syphilis transmission dynamics are considered.

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Introduction

The global burden of syphilis infection is high, with an estimated 10.6 million incident cases occurring annually.[1] Syphilis rates are rising among men who have sex with men (MSM) in the USA,[2] and similar trends in syphilis infections have been reported throughout Europe in cities with large populations of MSM.[3,4] Understanding the dynamics of syphilis transmission can provide insight into syphilis prevalence and incidence, and inform how to optimise prevention efforts to reduce the incidence of syphilis.

The rate of spread of syphilis in a population is related to the transmission probability per sexual partnership, the average rate of acquisition of sexual partners and the duration of infectiousness.[5] Prevention tools, such as condoms, risk-reduction counselling and syphilis screening and treatment, can alter syphilis rates by modifying these key parameters. In this paper, we will review the literature on syphilis transmissibility and susceptibility, discuss how prevention efforts can alter syphilis transmission and outline key unanswered questions and areas for future research.

Mode of syphilis transmission

Most cases of syphilis are transmitted by sexual contact (vaginal, anogenital and orogenital), but it can also be spread congenitally (*in utero* or less commonly during passage through the birth canal).[6–8] Rare cases of acquisition through blood products and organ donation have also been reported,[9–11] as have cases resulting from occupational and other exposures.[12–16]

Sexual transmission and transmission probability per sexual partnership

Sexual transmission accounts for most of the new cases of syphilis. The probability of syphilis transmission within a sexual partnership depends on many factors, including the frequency of sex, type of sexual contact (i.e. penile-vaginal, penile-anal or penile-oral), the stage of syphilis in the source patient, susceptibility of the partner and use of condoms.[17] Unbiased research on the probability of transmission between sexual partners is limited, and estimates are primarily inferred from studies that looked at either: (1) syphilis prevalence and incidence among named contacts to a known syphilis case; or (2) syphilis incidence among syphilis contacts participating in prospective trials of prophylactic therapy. These approaches have been used to estimate per-partnership syphilis transmission probabilities, and each approach has inherent biases and limitations (Table 1).

Several studies have reported syphilis prevalence and incidence among individuals named in contact investigation studies, primarily in the era before prophylactic treatment of contacts became standard of care. In 1941–1945 in Tennessee, von Werssowetz studied the prevalence and incidence of syphilis in identified contacts of patients with primary, secondary and early latent syphilis. Of note, the parameters for primary and secondary syphilis were not defined, and patients with early latent syphilis were classified as asymptomatic patients with a 'definite history of onset of syphilis of less than 4 years or, in the absence of this criterion, those who were under 30 years of age'. There were 927 contacts of primary and secondary syphilis for whom follow-up information was obtained, and syphilis was identified in 589 (64%). Of 1464 contacts who met their criteria for early latent syphilis, 809 (55%) were infected with syphilis.[18] In 1983 in the UK, Schober *et al*. interviewed contacts from the previous 12 weeks of patients with primary or secondary syphilis and reported the percentage who were diagnosed with syphilis either at the time of interview or in the 3 months following their last contact with the index syphilis case. Sixty-five of 127 contacts (51%) were infected with

Table 1. Estimates of syphilis transmission and limitations of available data

Type of study	Estimates of syphilis transmission	Sources of bias[20]
Prevalence and incidence among syphilis contacts	51–64% per partnership[18,19]	• Baseline seroprevalence of contacts will vary depending on population • Unclear identification of index patient • Overrepresentation in studies of infected sex partners already accessing health services • Inclusion of sex partners throughout the greatest time period that the index patient could have been infectious • Contacts who already had clinical signs of syphilis or who had reactive syphilis serology were excluded
Incidence among syphilis contacts	9–62% per partnership[21–23]	

syphilis. This study stratified the patients by gender of sex partner, and there was no difference found in the incidence of syphilis between heterosexual contacts (58%) and homosexual contacts (49%). In addition, 58% of contacts of patients with primary syphilis were infected, and 46% of contacts of patients with secondary syphilis were infected; this difference was not significant.[19]

These studies are subject to considerable bias, and Garnett *et al.* outline several issues with the assumptions used to derive transmissibility estimates from contact investigations. These include unclear identification regarding which partner was the index partner (creating bias towards overestimation of the probability of transmission), overrepresentation in studies of infected sex partners already receiving healthcare services (leading to selection bias overestimating transmission probability) and inclusion of sex partners throughout the greatest time period that the index patient could have been infectious (leading to inclusion of sex partners that may have had sexual contact with the index patient before the actual infectious period, which would cause an underestimation of the probability of transmission).[20] In addition, seroprevalence among named contacts varies depending on the background prevalence of disease and sexual behaviours of the at-risk population – factors that change considerably depending on local epidemiology.

Studies that measure syphilis incidence in untreated, seronegative contacts exposed to a known syphilis case have also been used to estimate per-partnership syphilis transmission risk. In 1949, Alexander and Schoch published their experience in treating – and not treating – contacts of patients with syphilis; they included individuals who were exposed to primary or secondary syphilis and had negative syphilis serologies and no clinical signs of syphilis. Of the 161 individuals in the control group, 100 (62%) became seropositive or developed clinical signs of syphilis.[21] There was no difference in the development of clinical signs of syphilis or seropositivity between contacts exposed to primary syphilis and those exposed to secondary syphilis.[21] In 1963, Moore *et al.* reported that 9% of seronegative syphilis contacts treated with placebo developed syphilitic lesions or became seropositive over the 3-month observation period.[22] Furthermore, in 1971, Schroeter *et al.* published an evaluation of prophylactic therapy for syphilis in a placebo-controlled trial. Patients were included if they were exposed to syphilis within the previous 30 days, and had no clinical signs or symptoms of disease and a non-reactive Venereal Disease Research Laboratory (VDRL) test. Of the 57 patients observed for 90 days who received placebo, 16 (28%) developed clinical signs of syphilis or a positive syphilis serology.[23] These studies must be considered with caution, as contacts who already had signs or symptoms of syphilis infection or who had reactive syphilis serology were excluded, which may have resulted in an underestimate of transmission.[20] With all the caveats delineated above, syphilis transmission between partners has been estimated as ranging from 9 to 64%.[20]

Unlike HIV,[24] data available about the per-act transmission risk of syphilis are very limited and based on imperfect estimates of per-partnership transmission probabilities and number of sex acts per year. Given these constraints, Gray *et al.* estimated a syphilis transmission probability of 0.5–1.4% per sexual act among MSM. They assumed a higher transmission of syphilis in penile-anal sex (1.4% transmission probability per act) and a lower transmission of syphilis in penile-oral sex (1.0% transmission probability per act) during primary and secondary syphilis. They estimated the same transmissibility during primary and secondary syphilis and that transmission during the early latent stage would be half that of transmission during primary and secondary syphilis.[25]

Lastly, unethical studies that addressed syphilis transmission have been conducted. In the 1940s in Guatemala, the US Public Health Service intentionally inoculated and exposed prisoners, sex workers and patients in a mental institution with infectious syphilis and subsequently estimated transmission probabilities.[26] In the 1950s, Magnuson *et al.* also described the inoculation of human 'volunteer' prisoners with syphilis.[27] It is difficult to draw many conclusions about syphilis transmission probabilities from these efforts given the methods used. In addition, these studies and others remind us of the absolute imperative of informed consent and ethical review.

Vertical transmission

Despite its preventable nature, congenital syphilis remains regrettably common in many parts of the world. Most cases of syphilis transmission during pregnancy are thought to occur *in utero* transplacentally, although transmission during birth is possible.[28] A study from 1952 by Fiumara *et al.* states that nearly all pregnant women with untreated primary or secondary syphilis will experience adverse outcomes, with half experiencing premature births, neonatal deaths and stillbirths, and half giving birth to infants with congenital syphilis. The mother's chance of transmission decreased somewhat with untreated early latent syphilis (with 20% prematurity, 4%

neonatal deaths, 10% stillbirths, 40% infants born with congenital syphilis and 20% of infants born full-term without evidence of syphilis). With untreated late latent syphilis, an estimated 10% of infants born would have congenital syphilis and 10% would be stillborn.[29] More recently, Sanchez *et al.* noted evidence of infection in all eight of eight infants born to mothers with untreated primary or secondary syphilis; of 11 infants born to mothers with untreated early latent syphilis, six (55%) showed evidence of infection.[30] Transmission to the fetus *in utero* has also been documented, with 16 of 24 fetuses (66%) exhibiting abnormal ultrasounds and 14 of 22 fetuses (64%) with *Treponema pallidum* detected in amniotic fluid.[31] Furthermore, testing has revealed that infection can be present in the amniotic fluid as early as 17 weeks gestational age,[32] supporting the theory that infection of the fetus can occur at any time during pregnancy.[28,33]

Transmission via blood products and organ donation

Syphilis transmission has occurred via blood transfusion in the past; however, since the implementation of screening of the blood supply and refrigeration of blood products, it is believed to be very rare.[11] Case reports do exist, including one in Ghana, which described a seroconversion in a child after receipt of a Rapid Plasma Reagin (RPR)-reactive unit of blood (screening of the blood supply was not conducted at this centre). The authors noted that the unit had been refrigerated for just 1 day, and that a longer period of refrigeration was likely to be necessary to kill *T. pallidum*.[10] Other case reports describe the likely transmission of syphilis after transfusion of fresh blood products that had negative syphilis serological assays at the time of transfusion.[9,34] More recently, reports of outcomes among recipients of syphilis-positive organ donors have been published,[35–37] and seroconversion has been documented following liver transplantation from an infected deceased donor despite the administration of post-exposure prophylaxis in the recipient.[37] The organ recipient remained asymptomatic, and syphilis infection in the donor is not considered a contraindication to solid organ transplantation.[37] Occupational exposure to syphilis via accidental injury with a scalpel has been described and is another potential mode of transmission via blood.[38]

Other transmission

Prior to the standard practice of using gloves by healthcare providers, there were reports of extragenital syphilitic lesions on the fingers and in the nose of physicians.[12,39] In addition, the transmission of syphilis via human bite in both sexual and non-sexual circumstances has been reported,[13–15] as well as transmission via mouth-to-mouth feeding of infants with pre-chewed food from infected relatives.[16]

Susceptibility to syphilis infection

The probability of syphilis transmission is also dependent on susceptibility in the exposed partner. Individuals with untreated syphilis are thought not to be able to acquire a new, symptomatic syphilis infection;[20,40] however, studies and experience have demonstrated that humans can be re-infected with syphilis after successful treatment.[41–43] The biological mechanisms underlying repeat infections and the lack of durable immunity in humans remain an area of research.[44] While long-acting benzathine penicillin is thought to provide a buffer of protection against re-infection for at least 3 weeks after treatment,[45,46] immune memory may not have sufficient time to develop when early syphilis is treated promptly.[20] Lastly, multiple studies have shown that HIV infection is a risk factor for repeat syphilis; whether this is a result of biological susceptibility or sexual behaviours and networks is unclear.[41–43]

Key prevention interventions and how they modify syphilis transmissibility and susceptibility

Syphilis screening of individuals at elevated risk, prompt treatment of syphilis and contact investigation and prophylactic treatment of exposed contacts are the cornerstones of syphilis control. These strategies decrease the probability of transmission per partnership as well as the duration of infectiousness. Other preventive strategies, including risk-reduction counselling to decrease the number and concurrency of sexual partners and increase condom usage, are also critical. Novel approaches, for instance, daily antibiotic pre-exposure prophylaxis for those at risk, are also under study (Table 2).

Testing

Screening of individuals at high risk for contracting syphilis is required to identify infections and halt further transmission. Gray *et al.* modelled the transmission of syphilis throughout a sexually active population of gay men to estimate the impact of various interventions to decrease syphilis in this community; their model predicted that increasing the frequency of testing and increasing testing among men who previously have not

Table 2. Syphilis prevention strategies and potential impact on syphilis transmission dynamics (Basic reproductive number $R_0 = \beta c D$)[5]

Prevention strategy	Transmission per partnership (β)	Rate of change of sexual partners (c)	Duration of infectiousness (D)
Screening	↓	No effect	↓
Condoms	↓	No effect	↓
Risk-reduction counselling	↓	↓	No effect
Treatment of cases	↓	No effect	↓
Contact investigation and empiric treatment of contacts	↓	No effect	↓
Antibiotic prophylaxis and selective mass treatment of high-risk individuals	↓	No effect	↓

been tested could reduce the incidence of syphilis.[25] Modelling in HIV-positive MSM suggested that more frequent syphilis screening or greater screening coverage of previously unscreened individuals would be cost-effective.[47] By routinely including syphilis serology in the standard monitoring blood tests performed for HIV-positive MSM at the Melbourne Sexual Health Centre, the proportion of MSM diagnosed with asymptomatic early syphilis increased significantly compared with the period before the routine inclusion of syphilis serology in HIV blood work. This change in procedure was thought to lead to increased identification of cases of infectious syphilis, increased treatment and the subsequent likely decrease in the duration of infectiousness and potential for further transmission among these men.[48] Reminder interventions have been shown to be effective in increasing testing; these include computer alerts to prompt clinicians to test high-risk MSM[49] and text messages to increase sexually transmissible disease (STD) re-testing rates.[50]

Treatment

Treatment of infected individuals and their exposed partners

Syphilis is very sensitive to treatment with penicillin, and benzathine penicillin is the treatment of choice.[51] *T. pallidum* has a long incubation period, thus treatment of patients, contact investigation and prophylactic treatment of asymptomatic-exposed contacts can abort ongoing spread of infection.[46] Identifying partners of syphilis cases and facilitating their prophylactic treatment can be challenging and labour-intensive for health departments, given the high numbers of anonymous sexual partners and partners met online among MSM with syphilis.[52] Using the Internet and text messaging to notify partners of syphilis cases is an important tool to identify incident syphilis cases and treat contacts in the modern syphilis epidemic.[53,54] Treatment of the infected mother during pregnancy can significantly reduce the chance of congenital syphilis,[31,40] and identifying and treating pregnant women with syphilis is a public health priority.

Mass treatment of syphilis and pre-exposure antibiotic prophylaxis

Epidemiologic mass treatment of individuals at high risk for syphilis in outbreak settings has been used as a community-level control measure to alter the course of syphilis epidemics.[55] In a 1976 epidemic in Fresno, California, in which 60% of cases were occurring among commercial sex workers and seasonal farm workers, and traditional disease control measures were not stemming the outbreak, commercial sex workers (CSWs) were asked to voluntarily engage in a treatment program. CSWs were offered benzathine penicillin before syphilis test results, and asked to regularly return to the clinic at 6–10-week intervals to be evaluated and treated. In the year after the treatment intervention was implemented, syphilis cases declined by 51% among CSWs and by 27% among seasonal farm workers.[45] A differing experience was described by Rekart *et al.*; a program offering mass azithromycin (1.8 g orally in a single dose) treatment to high-risk individuals was instituted during an outbreak in Vancouver, but resulted in only a transient decline in syphilis infections in 2000. They hypothesised that a sustained reduction in syphilis was not achieved because of the inability to reach and treat a sufficient proportion of the population at highest risk.[56] During a syphilis outbreak in 2000, mass presumptive azithromycin (1 g orally in a single dose) treatment was offered to all incarcerated MSM in Los Angeles County Men's Central Jail, and was accepted by 94%; effectiveness of the intervention was not able to be evaluated.[57]

The acceptability of single-dose epidemiologic mass treatment and ongoing antibiotic pre-exposure prophylaxis in individuals at high risk for disease has been studied on a limited basis. Antibiotic prophylaxis with intramuscular penicillin has been found to be acceptable in a high-risk population in Louisiana.[58] In an online survey conducted among MSM in Australia, over 50% of respondents stated that they would be likely to take daily pills to decrease their personal chance of syphilis infection, and over 75% were willing to take daily medication if it would result in a decrease in syphilis infections in the gay community.[59] A recent pilot study found that a daily dose of doxycycline to prevent syphilis infection in high-risk MSM was well-tolerated and that medication adherence was high.[60] Mathematical modelling of ongoing antibiotic prophylaxis in high-risk MSM has supported the effectiveness of such an intervention in significantly reducing new cases of syphilis in a community for a period of time, with a likely rebound in cases following discontinuation of the intervention.[59]

In syphilis epidemics occurring in defined populations, mass selective treatment and ongoing antibiotic pre-exposure prophylaxis may be both effective and acceptable as an option for syphilis control for a finite period of time; however, it should be undertaken with caution given the potential impact on subsequent rebound in infections following cessation of the intervention[61] and on antibiotic resistance. The possible effect on gonorrhoea of using azithromycin or doxycycline for syphilis prophylaxis is of particular concern, given *Neisseria gonorrhoeae*'*s* adeptness at developing resistance. If such an intervention were ever to be adopted on a larger scale, targeted administration to high-risk individuals would be critical.

Condoms

Latex condoms offer protection against syphilis transmission when used consistently and correctly but require that the condom cover the ulcer or condyloma latum entirely.[3] Mathematical modelling of disease-specific infectivity per act has supported the logical premise that the effectiveness of condoms decreases as individuals experience an increasing number of sexual exposures, particularly for diseases such as syphilis that can be transmitted via skin-to-skin contact.[62] In 2009, Koss *et al.* published a systematic review of studies that evaluated condom use and the risk of syphilis. They found that there were substantial limitations in the majority of studies reviewed; of the two studies that longitudinally assessed condom use and the risk of syphilis, there were trends (one of which was statistically significant) towards reduction in incident syphilis in those who used condoms consistently.[63] As an alternative option to the male condom, expanding

availability of the female condom (which can be used both for penile-vaginal and penile-anal intercourse) may provide a route to increase the amount of sex that is protected in a community.[64] Furthermore, given the increased skin coverage offered by the female condom for both vaginal and anal sex, this mode of protection may deliver an enhanced degree of protection for syphilis and other STDs transmitted via skin.

Sexual risk behaviour and risk-reduction counselling

Risk-reduction counselling is one of the major tenets of prevention and control of STDs. Asking patients about their sexual practices, partners and STD history, educating them about sexual risk behaviour and counselling about ways to reduce risk, remain a foundation of sexual health promotion. Given that concurrency, or the practice of having sexual partners that overlap in time, has been identified as a strong risk factor for syphilis transmission,[65,66] healthcare providers should ask patients if they believe that their partner has had another partner. This information can be used as an opportunity to educate about the risk associated with concurrency. The availability of Internet sites and mobile applications for meeting sex partners that facilitate a high rate of sexual partner change and concurrency, particularly among MSM,[53,67] signals that healthcare providers should ask patients about how they meet their partners and counsel them about limiting the number of sex partners. Sexual behaviours among MSM with and without HIV, including serosorting and other seroadaptive behaviours, have emerged as a potential driver of the increase in syphilis in this population;[68–70] it is not known if the availability of pre-exposure prophylaxis for HIV will lead to additional changes in sexual behaviour and in condom use among some MSM.[71,72] And last, among men at highest risk, it is not clear that behavioural interventions to increase condom use or reduce numbers of partners would be successful in achieving behaviour change or decreasing syphilis incidence.[73–75]

Unanswered questions

Many unanswered questions remain about syphilis transmission in the modern era, including updated estimates of transmissibility for primary and secondary syphilis by type of sexual contact. Uncertainties surround whether latent disease is infectious and the duration of infectiousness. There are numerous questions about host immunity, and how treatment at varying stages of infection modifies the risk of re-infection, influences the population of susceptible individuals and affects epidemic spread.[20] The potential role of antibiotic prophylaxis in preventing syphilis in high-risk individuals remains under study. And finally, given the role of sexual risk behaviour in driving syphilis transmission, there is a need for additional clarity regarding how best to support and encourage healthy sexual behaviours among populations at risk for syphilis.

Conclusions

Public health experience and historic studies illustrate that syphilis is highly transmissible during primary and secondary syphilis, and can be transmitted in a variety of ways including via sexual encounters, vertical transmission, parenteral exposures and occupational exposures. Rising rates of syphilis in MSM, despite years of syphilis elimination efforts, reflect how challenging it is to control the epidemic and underscore the need for intensified and novel prevention efforts. The global burden of syphilis infection remains high, and the public health system must maintain vigilance in responding to this epidemic to stem the negative outcomes associated with syphilis including advanced disease, increased risk of HIV transmission and acquisition, vertical transmission and congenital syphilis and cost to society associated with healthcare visits, treatments, disease investigation and partner services.

Conflicts of interest

None declared.

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