Published in final edited form as:

Curr Epidemiol Rep. 2018 March ; 5(1): 24–38. doi:10.1007/s40471-018-0138-z.

An Update on the Global Epidemiology of Syphilis

Noah Kojima[1] and **Jeffrey D Klausner**[1,2]

[1]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, 90095

[2]Fielding School of Public Health, University of California Los Angeles, Los Angeles, 90024

Abstract

Purpose of Review—Syphilis continues to cause morbidity and mortality worldwide. While syphilis infection is easily identifiable and treatable, rates of syphilis infection continue to increase among select populations in high-income countries and remain at endemic levels in low- and middle-income counties.

Recent findings—World Health Organization recommended strategies have led to the dual elimination of mother-to-child transmission of syphilis and HIV in several countries, however outbreaks among select populations need to be adequately addressed.

Summary—Continued vigilance and investment is needed to address syphilis worldwide. The epidemiology of syphilis differs in high-income and low- and middle-income counties.

Keywords

syphilis; Treponema pallidum; epidemiology; STI

Introduction

Each year, there are an estimated 6 million new cases of syphilis globally in persons aged 15 to 49 years [1-3]. Over 300,000 fetal and neonatal deaths are attributed to syphilis, with 215,000 additional infants placed at increased risk of early death [2].

In 2016, the World Health Organization (WHO) released a new strategy to combat sexually transmitted infections (STIs) from 2016 to 2021 [2]. The strategy prioritizes the elimination of congenital syphilis by implementing comprehensive syphilis screening and treatment among pregnant women, as well as in specific populations, with a goal of 90% reduction in syphilis incidence globally and 50 or fewer cases of congenital syphilis per 100,000 live births in 80% of countries by 2030.

Corresponding Author's Contact Information: Institutional address: David Geffen School of Medicine, University of California, Los Angeles, 10833 Le Conte Ave., Los Angeles, 90095; nkojima@ucla.edu; telephone: (310) 825-6373.

Conflict of Interest

Noah Kojima and Jeffrey D. Klausner each declare no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Despite prior efforts to eliminate syphilis in high-income countries [4, 5], budget reductions in STI programs and public health surveillance systems have undermined previous elimination and control efforts [6, 7]. Additionally, in Western Europe, the USA, and China, large increases in syphilis have been seen among key populations like men who have sex with men (MSM) [8, 9]. In low- and middle-income countries (LMICs) [10, 11], syphilis has remained endemic [12-15].

In recent years, with the discovery of HIV infection [16], and later, the identification of high rates of concurrence of HIV infection among those infected with syphilis [17-19], new attention has been put into understanding high rates of syphilis and HIV co-infection [20-23]. Considerable efforts have been made to eliminate mother-to-child-transmission of HIV and syphilis, which have been successful to date in five countries: Cuba, Thailand, Belarus, Armenia, and the Republic of Moldova [24, 25].

Syphilis continues to persist among MSM and other groups who tend to have multiple sex partners [26], and could likely return in heterosexual populations without public health vigilance. Because syphilitic lesions increase risk for acquiring and transmitting HIV infection, syphilis infections among MSM are of particular concern [27, 28]. The recent introduction of pre-exposure prophylaxis (PrEP) for HIV infection is a new tool for HIV prevention, however, with reports of high incidence of syphilis among PrEP users, clinicians and public health researchers need to stay vigilant to ensure that PrEP for HIV infection does not lead to increased syphilis transmission [29-32].

Microbiology

In 1905, Schaudinn and Hoffmann identified the causative agent of syphilis, *Treponema pallidum* [33, 34]. *T. pallidum* is a bacterium that is 0.10 to 0.18 micrometers in diameter and 6 to 20 micrometers in length [35]. At present, *T. pallidum* is unable to be reliably cultured on artificial media [36]. Additionally, *T. pallidum* is too slender to observe using direct light microscopy, so techniques like darkfield microscopy are used to visualize it [36, 37]. *T. pallidum pallidum*, the causative agent of syphilis, is closely related to other pathogenic strains of *T. pallidum*, which cause bejel, yaws, and pinta [38]. The four pathogenic strains of *T. pallidum* were indistinguishable until the recent discovery of a unique genetic signature of *tpp15* [39], a 5'-flanking region of a 15-kDa lipoprotein gene, which can be used to differentiate between strains [40].

Transmission

Syphilis is usually sexually acquired by direct skin-to-skin contact with someone with active primary or secondary lesions. Studies have shown the attack rate of syphilis within 30 days of sexual exposure to someone with syphilis is 16% to 30% [41, 42]. Although commonly thought of as a safer sexual practice, oral sex is an effective route for syphilis transmission [43-45]. Syphilis can also be transmitted congenitally, when spirochetes traverse the placenta of an infected women and infect the fetus [38]. Syphilis can be transmitted though transfused blood [46]. While blood borne transmission risk is nearly non-existent in high-income countries [47], it persists in low- and middle-income countries (LMICs; see LMIC list in the Supplemental Table) [48, 49].

Epidemiology

In the late 1990s, the prevalence of syphilis plummeted in many countries with endemic syphilis, largely thought to be due to the introduction of syndromic management for STIs [50, 51], behavioral changes, and the effect of AIDS mortality disrupting sexual networks [52-54]. However, since the introduction of antiretroviral therapy (ART), rates of syphilis have increased, especially among MSM, perhaps due to the reconstruction of sexual networks and increased frequency of sexual contact [55, 56].

General population prevalence data on syphilis are mostly limited to high-income countries. Especially among LMICs, currently available data likely underestimate the true burden of syphilis due to poor documentation and underreporting. Most country-representative data come from studies conducted among women at their first antenatal care visit and reported by the WHO [57].

Geographic distribution—Overall, the distribution of syphilis differs between LMICs and high-income countries (Figure 1, Table 1). Many LMICs have poor rates of syphilis testing among women at their first antenatal care visit, with many LMIC having fewer than 25% of women attending their first antenatal care visit tested for syphilis. LMICs generally have higher burdens of syphilis and the proportion of LMICs that treat over 75% of those diagnosed is lower than high-income countries. While high-income countries have concentrated epidemics of syphilis in specific populations, for example, MSM, transgender women, and sex workers, LMICs still have endemic rates of syphilis among their general populations [58-66]. The proportion of LMICs that have over 100 syphilis cases per 100,000 births is higher than high-income countries, which is likely attributable to failures of testing at the first antenatal care visit, endemic rates of syphilis, and failure to treat those who are diagnosed with syphilis. However, MSM, transgender women, and sex workers are disproportionately burdened with syphilis in all regions [17, 67-76]. Those specific groups are not targeted for testing and treatment like pregnant women at their first antenatal care visit, and therefore they do not benefit from testing and treatment for syphilis. Additionally those groups may suffer poor access to health care due to stigma and discrimination [77-79].

The studies listed below were conducted among different geographic regions and populations. Additionally the diagnostic assays for syphilis differed between studies. While syphilis estimates from those studies might not be directly comparable to each other because of differences in the sensitivity or specificity of each assay, when the variations in prevalence estimates by geography, population, or time are greater than 5%, those differences may be considered substantial.

Africa

A review of STIs among pregnant women reported that the prevalence of syphilis was 6.5% (95% confidence interval: 4.70-8.30) in Southern Africa, 4.6% (95% confidence interval: 3.7-5.4) in East Africa, and 4.0% (95% confidence interval: 1.7-6.3) in West Africa [80]. Another review and meta-analysis conducted among pregnant women attending antenatal care facilities in sub-Saharan Africa reported that the prevalence of syphilis was 4.5% (95%

confidence interval: 3.9-5.1) in East and Southern Africa and 3.5% (95% confidence interval: 1.8-5.2) in West and Central Africa [81].

North Africa—A study of syphilis trends in Morocco from 1995 to 2016 reported that the prevalence of active syphilis in 2016 was 0.56% among women 15 to 49 years declining from a prevalence of 1.8% in 1995 [82].

West Africa—Among 37,210 first time blood donations collected in Burkina Faso, West Africa during 2010, the overall seroprevalence of syphilis was 1.5%, with a higher rate of infection among men and donors in specific geographic regions [83]. A cross-sectional study conducted in Togo in 2011 among 1,106 female sex workers and 730 clients reported that the seroprevalence of syphilis among female sex workers was 2.2% and 2.3% among their clients [84]. Among female sex workers, syphilis was associated with age over 30 years, being married on in a relationship, being brothel based, and HIV infection. Among blood donations collected in Ghana from 2014 to 2015, 48% of transfusion facilities tested donors for syphilis with an estimated overall seroprevalence of 3.7% (95% confidence interval: 3.6-3.8) [85].

East Africa—In a study of 300 MSM in Tanzania, in Dar es Salaam, 2.5% of participants were exposed to syphilis and, in Tanga, 0% of participants were exposed to syphilis [86]. A study of 623 plantation migrant and non-migrant residents in Tanzania reported that syphilis prevalence among migrants was 12% versus 3% for non-migrant workers [87]. In Ethiopia, a study found that among 385 pregnant women in the Northwest, 11 (2.9%) women tested positive on a Treponema pallidum hemagglutination assay [88]. A retrospective analysis of 6,827 blood donors in Eastern Ethiopia, from 2010 to 2014 reported that the seroprevalence of syphilis among donations was 0.73% [89]. In Southern Ethiopia, among 993 HIV-infected participants, the seroprevalence of syphilis was 7.3% (95% confidence interval: 5.7-9.0), with the rate of infection higher among participants who were on antiretroviral therapy naïve, men, older than 50 years, had a primary school level of education, and had a history of a blood transfusion [90]. A cross-sectional study conducted in 2015 of 1,978 female sex workers in Rwanda reported that the overall prevalence of syphilis was 51.1%, with 27.4% of the cohort coinfected with syphilis and HIV [91].

Central Africa—A cross-sectional study conducted in Cameroon in 2014 among 7,069 pregnant women reported the prevalence of syphilis was 4% [92]. A study from Ngounie Province, Gabon conducted in 2010 among 10,580 pregnant women reported that the prevalence of syphilis was 2.5% [93]. The prevalence of syphilis increased with age and decreased with level of education.

Southern Africa—A study conducted in Maputo, Mozambique reported that among 1,380 participants that attended a youth clinic, the seroprevalence of syphilis was 0.36% (95% confidence interval: 0.15-0.84). A study conducted in Swaziland among 655 women aged 15 to 49 years reported that the prevalence of syphilis was 2.0% (95% confidence interval: 1.0-11.4) [94]. A study that extracted data from the National Health Laboratory Service database in Northern Cape Providence, South Africa from 2003 to 2012 reported that among 286,024 women of reproductive age, the seroprevalence of syphilis decreased from 8.6% in

2003 to 3.8% in 2011 [95]. A cross-sectional study of 2,293 sexually active, HIV-uninfected, non-pregnant women in Kwazulu-Natal reported that 56 (2.5%) participants were seropositive for syphilis [96]. A cross-sectional study of 200 MSM in Cape Town found that 21 (10%) study participants reported they had been previously treated for syphilis [97]. A study of female sex workers aged 18 years or older conducted from 2014 to 2015 in Port Elizabeth, South Africa reported that 20.3% (95% confidence interval: 16.3-24.2) tested positive for syphilis [98].

Australia

Overall rates of syphilis diagnoses have increased to 6.7 cases per 100,000 persons in 2012 [99]. Among the non-indigenous population of Australia, most cases of syphilis were reported among MSM. Those rates have increased by 20% from 2008 to 2012 among men aged 30 to 49 years. Among Aboriginal and Torres Strait Islanders, a syphilis outbreak was recorded in 2010 and 2015 with 790 associated syphilis cases among males and females [100]. Since 2011, 7 outbreak-associated cases of congenital syphilis were reported among those populations. A retrospective analysis of all blood donation testing from 2005 to 2010 from the Australian National Blood Service Donor Database found the prevalence of active syphilis increased over the study period among first-time and repeat blood donors [101].

China

A study on data from 2005 to 2014 from China's web-based infection surveillance system found that cases of syphilis had increased more than 3-fold from 135,210 in 2005 to 441,818 in 2014 and incidence of syphilis increased faster than 27 other notifiable infectious diseases that were recorded in their surveillance system (Figure 2a) [102]. In a retrospective study of 212,639 voluntary blood donors from 2010 to 2014 at the Shiyan Blood Transfusion Center and Hubei University of Medicine, the prevalence of positive syphilis serology was 0.57%, with higher rates seen among females and farmers [103]. Data collected from 19,750 MSM from 14 surveillance sites in Jiangsu between 2010 and 2014 showed the prevalence of syphilis decreased from 12.8% in 2010 to 6.5% in 2014 among resident MSM and migrant MSM; the prevalence of syphilis was consistently higher among migrant MSM versus resident MSM [104]. A cross-sectional study conducted among 15,705 MSM located in 8 cities in Shandong found a stable prevalence of syphilis from 2010 to 2014 (4.5% in 2014) and found that migrant MSM had higher rates of syphilis [105]. A cross-sectional study of 120,049 female sex workers from 2010 to 2015 in Guangxi found that the prevalence of syphilis decreased from 9.2% in 2010 to 7.3% in 2015 among low-tier female sex workers and 2.6% in 2010 to 1.4% in 2015 among high tier female sex workers [106]. Among clients of female sex workers the majority of syphilis cases occurred among older male clients. A study of 9,240 drug users attending a methadone maintenance treatment clinic from 2006 to 2014 found the rates of syphilis seroconversion to be 0.77 per 100 person-years (95% confidence interval: 0.62-0.93 per 100 person-years), with stable rates of infection though out the study period [107]. A cross-sectional study of 3,859 female drug users in Beijing conducted from 2010 to 2014 found 239 (6.2%) women tested positive for syphilis serology, an increase from 6.0% in 2010 to 8.8% in 2014 [108]. Syphilis prevalence was higher among synthetic drug users (7.9%) when compared to traditional drug users (3.7%).

Europe

Among syphilis cases reported for 29 European Union Member States (Figure 2b), the overall rate of syphilis and number of cases of syphilis among women has been decreasing (2.3 notifications per 100,000 women in 2008 to 1.6 notifications per 100,000 women in 2013), however the notification rate has increased among men from 6.5 notifications per 100,000 men in 2008 to 8.4 notifications per 100,000 men in 2013 [8, 109]. In 2013, men were five times more likely to have syphilis than women (8.4 notifications per 100,000 versus 1.6 notifications per 100,000) [109]. Additionally, most cases of syphilis were observed in people older than 25 years and 58% of cases were reported among MSM. France, Malta, and the Netherlands had the highest male-to-female ratio of syphilis cases, whereas Romania, Lithuania, and Estonia and the lowest. The proportion of total cases of syphilis was higher among MSM (58%) than heterosexual persons (36%). Among MSM, 34% of the syphilis cases had a HIV coinfection.

Belgium—Among people presenting to a HIV/STI clinic from 1992 to 2012 in Antwerp, the diagnosis of syphilis was made 729 times among 454 persons [55]. Of the cases, 445 of 729 (61%) infections occurred in people that had more than one syphilis infection and 10 HIV-infected MSM on antiretroviral therapy had over five syphilis infections during the study.

Bulgaria—In the Varna Region, 15 of 2,702 (0.56% [95% confidence interval: 0.28-0.84]) pregnant women tested between 2009 to 2013 had positive syphilis serology [110]. Rural inhabitants had a higher risk of infection in comparison to urban inhabitants.

Croatia—Among 387 MSM recruited at a University Hospital in Zagreb from 2010 to 2011, 7.6% of participants tested positive for syphilis with a Treponema pallidum hemagglutination assay [111].

Denmark—Among HIV-infected women that were followed in an outpatient setting from 2011 to 2012, 8 of 334 (2.4%) women had positive serologic tests for syphilis [112].

France—Among an observational cohort of intravenous drug users, sex workers, and homeless people recruited at 9 non-hospital screening centers, 6 of 341 (1.78%) participants had positive syphilis serology [113]. Five of the cases were intravenous drug users. In a study of patients who were diagnosed with syphilis in Montpellier, France from 2002 to 2011, 82% of cases were MSM [114]. A case-control study conducted in Lille found that condomless receptive oral sex (odds ratio: 4.86 [95% confidence interval: 1.63-14.48]) and use of anal sex toys (odds ratio: 2.72 [95% confidence interval: 1.01-7.32]) increased risk of syphilis infection [115]. In a national cross-sectional survey in New Caledonia[1] among persons aged 19 to 49 years, prevalence of latent syphilis was estimated to be 3% (95% confidence interval: 1.7-4.3) and active syphilis was estimated to be 0.4% (95% confidence interval: 0.0-0.9) [116].

[1]New Caledonia was included under the France sub-section because it is a special collectivity of France in the southwest Pacific Ocean.

Germany—From 2010 to 2015, the number of syphilis notifications increased by 19% to a total of 6,834 reported cases [117], mostly among MSM in larger German cities. Among a multicenter cohort of 1,843 MSM, syphilis incidence was 4.06 per 100 person-years [118]. Syphilis incidence was higher among MSM living in Berlin when compared MSM living in other cities. In another cohort of 503 HIV-infected MSM in Germany, 4.6% of the cohort had positive syphilis serology [119]. Among 1380 male clients attending a community-based voluntary counselling and testing site for MSM, 24 (1.7%) persons had positive syphilis serology [120]. Syphilis infection and rectal STIs were associated with increased risk for HIV infection. Among 9,284 female sex workers attending local public health departments in Germany, 1.1% of those tested had a positive test for syphilis serology [121]. Among 790 refugees and asylum seekers in Germany in 2015, only one case (0.1%) of syphilis was identified [122].

Greece—Among a retrospective analysis of 1,185 patients with confirmed primary syphilis in Athens from 2005 to 2012, the number of primary syphilis cases rose from 111 in 2005 to 158 in 2012 [123]. More men had syphilis than women and increasing numbers of cases were observed among MSM throughout the study (20.7% of cases in 2005 versus 59.1% of cases in 2010). In a cohort study of HIV-infected persons conducted at the University Hospital in Thessaloniki, 58 of 1,119 (5.2%) patients tested positive for syphilis serology [124], with the majority of cases being MSM (94.8%).

Greenland—In an observational cross-sectional study from 2010 to 2014 in Greenland, 94 cases of syphilis were reported among 51 males and 43 females [125]. Syphilis cases in Greenland increased from zero cases in 2010 to 95.7 cases per 100,000 persons in 2014.

Ireland—Among pregnant women in an antenatal and peripartum teaching hospital in Dublin from 2005 to 2012, 194 (0.28% of all pregnancies) women had positive syphilis serology [126].

Malta—Among 500 migrants screened from 2010 to 2011, the diagnosis of latent syphilis was made in 11 (2.2%) migrants [127]. The study recommended that syphilis should not be screened among asymptotic asylum seekers.

Moldova—Among a respondent driven sample of female sex workers conducted from 2009 to 2010, in Chisinau, 27 of 299 (8.4 [95% confidence interval: 5.2-11.6]) women, and, in Balti, 22 of 359 (6.1 [95% confidence interval: 3.9-8.2]) women tested positive for syphilis serology [128].

Netherlands—STI surveillance data collected from 2007 to 2011 indicated that 2,637 of 476,225 (0.6%) STI consultations tested positive for syphilis serology [129]. Among women and heterosexual men, rates were nearly 0% (120/228,605) and 0.1% (191/165,282), respectively, however 2,326 of 82,338 (2.8%) MSM showed syphilis seropositivity. National STI/HIV surveillance data on MSM collected from 2007 to 2015 showed that among HIV-infected and HIV-infected MSM, syphilis rates were high in 2007 (12.3% and 2.8%, respectively), decreased in 2011 (4.5% and 1.4%), and increased in 2015 (8.0% and 1.8%) [130]. Among Dutch blood donations that were screened for transfusion-transmissible

infections from 1995 to 2014, the prevalence of syphilis increased by 50% from the period of 1995 to 2002 (22.3 positive tests per 100,000 new donors) to 2003 to 2014 (32.8 positive tests per 100,000 new donors) [131]. Among 3,052 consultations for male sex workers in Dutch STI clinics from 2006 to 2012, 2.6% of male sex workers tested positive for syphilis, with no significant change in prevalence throughout the study [132]. Among 36,296 consultations for female sex workers from 2006 to 2013, the syphilis positivity rate decreased from 0.6% in 2006 to 0.1% in 2013 [133]. Syphilis diagnosis among those female sex workers was associated with prior STI diagnosis and several ethnicities.

Norway—A study of MSM that used data collected from the Norwegian Surveillance System for Communicable Diseases collected from 1995 to 2011 reported that from 1995 to 1999 there was one reported case of HIV and syphilis co-infection, however from 2001 to 2011 cases of HIV and syphilis co-infection increased to between 0 to 9 cases each year [134].

Poland—Among a retrospective analysis of syphilis cases in pregnant and non-pregnant women in Bialystok, Poland from 2000 to 2015, 47 cases were identified and treated [135]. Among those cases, 17 (36.2%) women were pregnant and 30 (63.8%) women were not pregnant. Most of those women lived in urban areas and were in long-standing relationships. Among male patients who had positive syphilis serology in the same city, 19 of 49 (38.8%) men identified as MSM and the majority were single and lived in urban areas [136]. In 2011, there were 841 cases of syphilis, with the highest rate of 4.7 per 100,000 in Mazowieckie district and the lowest rate of 0.2 per 100,000 cases in Swietokrzyskie district [137].

Portugal—Among a cohort of 580 patients with positive syphilis serology in Lisbon, Portugal, 75% of patients were male and 42% were co-infected with HIV [138].

Serbia—Among reported syphilis cases among ethically Roma people in Belgrade from 2010 to 2014, the average prevalence of syphilis among all reported subjects was 9.6% [139]. Heterosexual men made up the majority of cases.

Spain—In a population-based incidence study in Barcelona from 2007 to 2011, a total of 1,124 cases were detected [140]. Of those cases, 91.9% occurred among men and 80.7% of those men self-identified as MSM.

Slovak Republic—Among cases of syphilis reported to the National Health Information Center in the Slovak Republic from 1991 to 2013, the overall rate of syphilis was 4.21 per 100,000 persons [141]. Males had a higher prevalence of syphilis than females.

Ukraine—A study from a nation-wide multi-side randomly sampled health survey of prisoners being released within six months reported that 40 of 402 participants (10% [95% confidence interval: 7.4-13.2]) had positive syphilis serology [142].

United Kingdom—Surveillance data collected in sexual health clinics in England from 2005 to 2014 showed increased syphilis diagnoses among MSM and decreased syphilis diagnoses among non-MSM and women [143, 144]. From 2013 to 2014, cases of syphilis

rose by 46% among MSM (2,375 cases to 3,477 cases) [145]. That increase is thought to be due to high levels of condomless sex, particularly among men who are co-infected with HIV. Geospatial real-time networking applications influenced syphilis outbreaks among MSM [146]. From 2013 to 2014, 30 cases of syphilis were identified among mostly white MSM who had met sex partners with mobile applications [147]. Among men diagnosed with syphilis in London in 2013, there were up to 36 cases of syphilis (95% confidence interval: 34-38) per 100,000 men and 80% of those infected identified as MSM [148]; 40% of cases were found within 11 km of central London. During 2011 to 2014, MSM prescribed HIV post-exposure prophylaxis following sexual exposure had increased odds (adjusted odds ratio: 2.25 [95% confidence interval: 1.73-2.93]) of being diagnosed with syphilis in the last 12 months [149]. In 2011, among 2,704 women who identified as sex workers attending genitourinary medicine clinics in England 3 of 2,380 (0.1%) tested seropositive for syphilis, which was comparable to other non-sex worker female clinic attendees (285 of 466,248 [0.1%]) [150]. Among children born in the United Kingdom between 2010 and 2015, 17 cases of congenital syphilis were identified [151], the rate of cases was below the WHO elimination threshold.

Latin America

A review of STIs among pregnant women reported that the prevalence of syphilis was 2.6% (95% confidence interval: 1.2-3.9) in Latin America. In a cohort of 312 MSM and 89 male-to-female transgender women in Lima, Peru, the prevalence of active syphilis was 16.8% among MSM and 6.7% among transgender women, and both groups had a high prevalence of HIV coinfection [152]. A cohort study of 391 MSM in Rio de Janeiro, Brazil reported their prevalence of syphilis was 9.9% [153]. A retrospective study conducted among 1,150 men with HIV-infection in Buenos Aires, Argentina reported a syphilis incidence of 14.9 cases per 100 patients per year [154]. Most of the participants were MSM.

USA

After a syphilis outbreak in the early 1990s, syphilis rates decreased to 2.1 cases per 100,000 persons in 2000 and 2001, the lowest rates of recorded syphilis in the USA [155]. However, since then, the rate of primary and secondary syphilis increased (Figure 2c). That increase is attributed to increased cases of syphilis among MSM [156]. In 2013 to 2016, the rate of syphilis increased among both men and women, which led to increased numbers of cases of congenital syphilis since 2013 [155]. During 2015 to 2016, rates of primary and secondary syphilis have increased in every age group over 15 years, in every race, ethnicity, and region. In 2016, rates of primary and secondary syphilis are higher among men (15.6 cases per 100,000 males) than women (1.9 cases per 100,000 females). Among the 27,814 reported cases of primary and secondary syphilis in 2016, 16,155 (58.1%) cases occurred among MSM. The percent of HIV-coinfection was 47.0% for MSM, 10.7% for men who have sex with women, and 4.1% for women. Black Americans had 23.1 cases per 100,000 persons, Native Hawaiians/Other Pacific Islanders had 12.9 cases per 100,000 persons, Hispanics Americans had 10.9 cases per 100,000 persons, American Indians/Alaska Natives had 8.0 cases per 100,000 persons, White Americans had 4.9 cases per 100,000 persons, and Asian Americans had 3.9 cases per 100,000 persons.

Prevention, screening, and treatment

While syndromic management has been a useful method for the treatment of STIs at the individual level [157-159], because most cases are asymptomatic, the lack of routine screening and diagnostic testing misses most cases of syphilis [160, 161]. Increased use of dual point-of-care HIV and syphilis tests, which are sensitive and specific [162-166], increase equity and access to testing and facilitate faster treatment and partner care [161, 167, 168]. Strategies implemented for the dual elimination of mother-to-child-transmission of HIV and syphilis, which includes first antenatal care visit screening, led to increased efforts to reach proposed goals for control [2]. Implementation of widespread, public health efforts (i.e., mandatory syphilis testing among pregnant women and within businesses and educational institutions) have been proven to be effective in controlling syphilis [169]. However, as public health efforts wane, syphilis prevalence increases [145, 170, 171].

An Australia study provides evidence that increased targeted screening for syphilis is associated with increased detection of asymptomatic infectious syphilis and decreased secondary syphilis among HIV-infected and HIV-uninfected MSM in a national setting [172]. However, this model needs to be implemented and replicated in other countries to show reproducibility.

Partner treatment

Partner treatment is an effective way to manage syphilis outbreaks among heterosexual patients [173]. Addressing partner treatment among MSM has traditionally been more difficult, especially due to the high proportion of sexual contacts that may be anonymous and facilitated by social media. However, studies have shown success in using Internet-based methods to identify, locate, test, and treat anonymous sex partners [174].

Benzathine Benzylpenicillin Shortage

Benzathine benzylpenicillin, a WHO essential medicine [175], is needed for syphilis treatment, however, shortages of the drug have been reported in many regions since 2015 [176, 177]. There have been reports of shortages of benzathine benzylpenicillin in high syphilis morbidity countries [178]. That shortage could lead to poorer or no treatment of pregnant women with syphilis [179]. If syphilis screening coverage was ≥95% for 30 high syphilis burden countries, an estimated 712,030 women would require treatment of at least one injection of 2.4MU of benzathine benzylpenicillin [180]. Adequate supplies of this life-saving drug must be made available for global treatment of syphilis.

Resistance

Some providers opt to use second-line oral antibiotics, like macrolides and tetracyclines to treat early syphilis, however, there are reports of clinically significant macrolide-resistant *T. pallidum* [181-189], which is especially relevant in light of the shortage of benzathine benzylpenicillin. In fact, macrolide-resistance syphilis is present in many geographic regions including Australia, Canada, China, Europe, and the USA [181-189]. Currently, macrolide-resistant strains of syphilis seem to be uncommon in southern Africa and Taiwan [190-193].

Prevention

A pilot study of daily doxycycline prophylaxis for bacterial STIs among HIV-infected MSM found that daily doxycycline users had reduced incidence of syphilis infections [194]. A larger randomized control study of on-demand post-exposure prophylaxis with doxycycline among MSM that were not infected with HIV found that doxycycline use after sexual activity "post-exposure" reduced the incidence of syphilis infections [195]. Prior studies on periodic presumptive treatment of syphilis among sex workers have produced mixed findings [196]. Such innovative methods in prevention of syphilis as chemoprophylaxis could be used among core groups like sex workers and PrEP users.

Syphilis Vaccine

There have been many attempts to create a vaccine for syphilis, yet none have been effective to date [197]. The development of a syphilis vaccine has the potential to greatly reduce morbidity and mortality caused by congenital syphilis and could have lasting protective effects that could greatly benefit vaccinated populations [198]. A new syphilis vaccine candidate has recently been described that shows promise among animal models, however the efficacy has yet to be determined among people [199]. Investments in syphilis biology and immunology should be strengthened.

Conclusions

Syphilis continues to cause morbidity and mortality and its prevalence is increased among select populations. In high-income countries, important metrics like screening at the first antenatal care visit and rates of congenital syphilis are high, however current syphilis control strategies are ignoring key populations, i.e., MSM, transgender women, and sex workers. Current studies show that syphilis incidence is increasing in those key communities. Among many LMICs, syphilis continues to remain at endemic levels in the general population; however better reporting data are needed to properly estimate prevalence of syphilis and its associated morbidity and mortality. In addition, looking at temporal trends from current data, the proportion of LMICs testing and treating pregnant women at their first antenatal care visit is improving, but high rates of congenital syphilis infections continue. While the elimination of mother-to-child-transmission of HIV and congenital syphilis in five nations is a major success, syphilis prevalence is increasing among select groups, macrolide-resistant syphilis is being identified in more geographic areas, and there are shortages of benzathine benzylpenicillin which provide the opportunity for the resurgence of syphilis. Programs need to get back to the basics by investing in public health infrastructure and human resources, improving testing and routine screening, ensuring a strong medication supply, providing treatment for identified cases, encouraging partner treatment, and innovating with new strategies like prophylactic medication and vaccines. As the Abraham Lincoln, who allegedly was infected with syphilis said, "You cannot escape the responsibility of tomorrow by evading it today [200, 201]."

Acknowledgments

We would like to thank Mr. Maanda Mudau for comments. NK is supported by the Fogarty International Center of the National Institutes of Health (NIH) under award number D43TW009343 and the University of California

Global Health Institute (UCGHI). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or UCGHI.

Funding sources

Time for literature review and manuscript preparation was supported in part by NIH/FIC D43TW009343 (Fogarty International Center of the NIH and the University of California Global Health Institute Training Program), NIH P30MH058107 (The Center for HIV Identification, Prevention, and Treatment Services), and NIH/NIAID AI028697 (UCLA Center for AIDS Research). No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

Papers of particular interest, published recently, and have been highlighted as:

- • Of importance
- •• Of major importance

1•. Newman L, Rowley J, Vander Hoorn S, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. PloS one. 2015; 10(12):e0143304. A recent systematic review of the prevalence and incidence of STIs. [PubMed: 26646541]

2••. World Health Organization. Global Health Sector Strategy on Sexually Transmitted Infections 2016-2021. 2016 The WHO's strategy for STI treatment.

3••. World Health Organization. Report on global sexually transmitted infection surveillance 2015. 2015 WHO prevalence estimates and commentary.

4. Centers for Disease Control and Prevention. The National Plan to Eliminate Syphilis from the United States. 2006

5••. World Health Organization. Investment case for eliminating mother-to-child transmission of syphilis: promoting better maternal and child health and stronger health systems. 2012 WHO's strategy to address EMTCT of syphilis.

6. Clement ME, Hicks CB. Syphilis on the Rise: What Went Wrong? JAMA. 2016; 315(21):2281–3. [PubMed: 27272579]

7. Golden MR, Kerndt PR. Improving clinical operations: can we and should we save our STD clinics? Sex Transm Dis. 2010; 37(4):264–5. [PubMed: 20182405]

8. Abara WE, Hess KL, Neblett Fanfair R, Bernstein KT, Paz-Bailey G. Syphilis Trends among Men Who Have Sex with Men in the United States and Western Europe: A Systematic Review of Trend Studies Published between 2004 and 2015. PloS one. 2016; 11(7):e0159309. [PubMed: 27447943]

9. Chen G, Cao Y, Yao Y, et al. Syphilis incidence among men who have sex with men in China: results from a meta-analysis. Int J STD AIDS. 2017; 28(2):170–8. [PubMed: 26992411]

10. Stamm LV, Mudrak B. Old foes, new challenges: syphilis, cholera and TB. Future Microbiol. 2013; 8(2):177–89. [PubMed: 23374124]

11. World Bank. [18 Oct] GNI per capita, Atlas method (current US$). Available at: https://data.worldbank.org/indicator/NY.GNP.PCAP.CD

12. Dennie CC. A history of syphilis. Springfield, Ill: Charles C. Thomas; 1962.

13. Oriel JD. The scars of venus. London, England: Springer-Verlag; 1994.

14. U.S. Department of Health, Education and Welfare. Syphilis, a synopsis. Washington, D C: Government Printing Office; 1968. PHS publication 168 U. S

15. Quetel C. History of syphilis. England: Blackwell Scientific Publications Ltd; 1990.

16. Centers for Disease Control and Prevention. Pneumocystis pneumonia--Los Angeles. MMWR Morb Mortal Wkly Rep. 1981; 30(21):250–2. [PubMed: 6265753]

17. Centers for Disease Control and Prevention. Primary and secondary syphilis among men who have sex with men--New York City, 2001. MMWR Morb Mortal Wkly Rep. 2002; 51(38):853–6. [PubMed: 12363336]

18. Centers for Disease Control and Prevention. Primary and secondary syphilis--United States, 2003-2004. MMWR Morb Mortal Wkly Rep. 2006; 55(10):269–73. [PubMed: 16543880]

19. Division of STD Prevention. Syphilis Surveillance Report: Sexually transmitted diseases surveillance 2004 supplement: syphilis surveillance report. Services DoHaH; Atlanta, Georgia: 2005.

20. Paz-Bailey G, Meyers A, Blank S, et al. A case-control study of syphilis among men who have sex with men in New York City: association With HIV infection. Sex Transm Dis. 2004; 31(10):581–7. [PubMed: 15388994]

21. Katz MH, Schwarcz SK, Kellogg TA, et al. Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. Am J Public Health. 2002; 92(3):388–94. [PubMed: 11867317]

22. Kim AA, Kent CK, Klausner JD. Increased risk of HIV and sexually transmitted disease transmission among gay or bisexual men who use Viagra, San Francisco 2000-2001. AIDS. 2002; 16(10):1425–8. [PubMed: 12131222]

23. Wong W, Chaw JK, Kent CK, Klausner JD. Risk factors for early syphilis among gay and bisexual men seen in an STD clinic: San Francisco, 2002-2003. Sex Transm Dis. 2005; 32(7):458–63. [PubMed: 15976605]

24••. Ishikawa N, Newman L, Taylor M, Essajee S, Pendse R, Ghidinelli M. Elimination of mother-to-child transmission of HIV and syphilis in Cuba and Thailand. Bull World Health Organ. 2016; 94(11):787–A. Countries that successful implemented EMTCT for syphilis and HIV. [PubMed: 27821878]

25. World Health Organization. WHO validates countries' elimination of mother-to-child transmission of HIV and syphilis. 2016

26. Hiransuthikul A, Prawepray N, Pengpum S, Reankhomfu R, Panpet P, Mahachokchai N, Sumalu S, Brutat P, Sungsing T, Janamuaysook R, Pengnonyang S, Jantarapakde J, Trachunthong D, Nakorn PR, Charoenying S, Phanuphak P, Vannakit R, Phanuphak N. IDWeek 2017. San Diego, California: 2017. Similar Sexually Transmitted Infections Prevalence Despite Lower HIV Prevalence Among Transgender Women Compared to Men Who Have Sex With Men in Thai Community-based Test and Treat Cohort.

27. Galvin SR, Cohen MS. The role of sexually transmitted diseases in HIV transmission. Nat Rev Microbiol. 2004; 2(1):33–42. [PubMed: 15035007]

28. Ho EL, Lukehart SA. Syphilis: using modern approaches to understand an old disease. J Clin Invest. 2011; 121(12):4584–92. [PubMed: 22133883]

29. Kojima N, Davey DJ, Klausner JD. Pre-exposure prophylaxis for HIV infection and new sexually transmitted infections among men who have sex with men. AIDS. 2016; 30(14):2251–2. [PubMed: 27314179]

30. Liu AY, Cohen SE, Vittinghoff E, et al. Preexposure Prophylaxis for HIV Infection Integrated With Municipal- and Community-Based Sexual Health Services. JAMA Intern Med. 2016; 176(1):75–84. [PubMed: 26571482]

31. Volk JE, Marcus JL, Phengrasamy T, et al. No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting. Clin Infect Dis. 2015; 61(10):1601–3. [PubMed: 26334052]

32. Fata LL, Cotte L, Godinot M, Pansu A, Groslafeige C, Makhloufi D, Boibieux A, Ferry T, Chidiac C. IDWeek 2017. San Diego, California: 2017. High Asymptomatic STI Prevalence and Incidence in French MSM Starting PrEP.

33. Schaudinn FR, Hoffmann E. Vorläufiger Bericht über das Vorkommen von Spirochaeten in syphilitischen Krankheitsprodukten und bei Papillomen. Arbeiten aus dem Kaiserlichen Gesundheitsamt. 1905; 22:527–34.

34. Waugh M. The centenary of Treponema pallidum: on the discovery of Spirochaeta pallida. Int J STD AIDS. 2005; 16(9):594–5. [PubMed: 16176623]

35. Norris SJ, L SA. Treponema and other host-associated spirochetes. In: Murray PR, B EJ, Pfaller MA, Tenover FC, Yolken RH, editorsManual of clinical microbiology. 6. Washington, D.C: ASM Press; 1995. 636–51.

36. Ratnam S. The laboratory diagnosis of syphilis. Can J Infect Dis Med Microbiol. 2005; 16(1):45–51. [PubMed: 18159528]

37. Larsen SA. Syphilis. Clin Lab Med. 1989; 9(3):545–57. [PubMed: 2676323]

38. Lafond RE, Lukehart SA. Biological basis for syphilis. Clin Microbiol Rev. 2006; 19(1):29–49. [PubMed: 16418521]
39. Noordhoek GT, Hermans PW, Paul AN, Schouls LM, van der Sluis JJ, van Embden JD. Treponema pallidum subspecies pallidum (Nichols) and Treponema pallidum subspecies pertenue (CDC 2575) differ in at least one nucleotide: comparison of two homologous antigens. Microb Pathog. 1989; 6(1):29–42. [PubMed: 2471912]
40. Centurion-Lara A, Castro C, Castillo R, Shaffer JM, Van Voorhis WC, Lukehart SA. The flanking region sequences of the 15-kDa lipoprotein gene differentiate pathogenic treponemes. The Journal of infectious diseases. 1998; 177(4):1036–40. [PubMed: 9534979]
41. Moore MB Jr, Price EV, Knox JM, Elgin LW. Epidemiologic Treatment of Contacts to Infectious Syphilis. Public Health Rep. 1963; 78:966–70. [PubMed: 14084872]
42. Schroeter AL, Turner RH, Lucas JB, Brown WJ. Therapy for incubating syphilis. Effectiveness of gonorrhea treatment. JAMA. 1971; 218(5):711–3. [PubMed: 5171497]
43. Centers for Disease Control and Prevention. Transmission of primary and secondary syphilis by oral sex--Chicago, Illinois, 1998-2002. MMWR Morb Mortal Wkly Rep. 2004; 53(41):966–8. [PubMed: 15496825]
44. Marcus U, Bremer V, Hamouda O, et al. Understanding recent increases in the incidence of sexually transmitted infections in men having sex with men: changes in risk behavior from risk avoidance to risk reduction. Sex Transm Dis. 2006; 33(1):11–7. [PubMed: 16385216]
45. Page-Shafer K, Shiboski CH, Osmond DH, et al. Risk of HIV infection attributable to oral sex among men who have sex with men and in the population of men who have sex with men. AIDS. 2002; 16(17):2350–2. [PubMed: 12441814]
46. Kaur G, Kaur P. Syphilis testing in blood donors: an update. Blood Transfus. 2015; 13(2):197–204. [PubMed: 25545876]
47. Gardella C, Marfin AA, Kahn RH, Swint E, Markowitz LE. Persons with early syphilis identified through blood or plasma donation screening in the United States. The Journal of infectious diseases. 2002; 185(4):545–9. [PubMed: 11865408]
48. Owusu-Ofori AK, Parry CM, Bates I. Transfusion-transmitted syphilis in teaching hospital, Ghana. Emerg Infect Dis. 2011; 17(11):2080–2. [PubMed: 22099108]
49. Adegoke AO, Akanni O, Dirisu J. Risk of transfusion-transmitted syphilis in a tertiary hospital in Nigeria. N Am J Med Sci. 2011; 3(2):78–81. [PubMed: 22540070]
50. Pettifor A, Walsh J, Wilkins V, Raghunathan P. How effective is syndromic management of STDs?: A review of current studies. Sex Transm Dis. 2000; 27(7):371–85. [PubMed: 10949428]
51. Johnson LF, Dorrington RE, Bradshaw D, Coetzee DJ. The effect of syndromic management interventions on the prevalence of sexually transmitted infections in South Africa. Sex Reprod Healthc. 2011; 2(1):13–20. [PubMed: 21147454]
52. Chesson HW, Dee TS, Aral SO. AIDS mortality may have contributed to the decline in syphilis rates in the United States in the 1990s. Sex Transm Dis. 2003; 30(5):419–24. [PubMed: 12916133]
53. Kenyon CR, Osbak K, Buyze J, Chico RM. The changing relationship between bacterial STIs and HIV prevalence in South Africa - an ecological study. Int J STD AIDS. 2015; 26(8):556–64. [PubMed: 25122576]
54. Kenyon CR, Osbak K, Chico RM. What underpins the decline in syphilis in Southern and Eastern Africa? An exploratory ecological analysis. Int J Infect Dis. 2014; 29:54–61. [PubMed: 25449236]
55. Kenyon C, Lynen L, Florence E, et al. Syphilis reinfections pose problems for syphilis diagnosis in Antwerp, Belgium - 1992 to 2012. Euro Surveill. 2014; 19(45):20958. [PubMed: 25411690]
56•. Kenyon CR, Osbak K, Tsoumanis A. The Global Epidemiology of Syphilis in the Past Century - A Systematic Review Based on Antenatal Syphilis Prevalence. PLoS Negl Trop Dis. 2016; 10(5):e0004711. [PubMed: 27167068]
57. World Health Organization. [18 Oct] Global Health Observatory data repository. Available at: http://apps.who.int/gho/data/node.main.A1357STI?lang=en
58. Ahmed HJ, Omar K, Adan SY, Guled AM, Grillner L, Bygdeman S. Syphilis and human immunodeficiency virus seroconversion during a 6-month follow-up of female prostitutes in Mogadishu, Somalia. Int J STD AIDS. 1991; 2(2):119–23. [PubMed: 2043703]

59. Killewo JZ, Sandstrom A, Bredberg Raden U, Mhalu FS, Biberfeld G, Wall S. Prevalence and incidence of syphilis and its association with HIV-1 infection in a population-based study in the Kagera region of Tanzania. Int J STD AIDS. 1994; 5(6):424–31. [PubMed: 7849121]
60. Kumar B, Rajagopalan M, Sehgal S, Sharma M, Malhotra S. Syphilis serology and human immunodeficiency virus positivity in Chandigarh. Int J STD AIDS. 1990; 1(6):438–9. [PubMed: 2094408]
61. Kunawararak P, Beyrer C, Natpratan C, et al. The epidemiology of HIV and syphilis among male commercial sex workers in northern Thailand. AIDS. 1995; 9(5):517–21. [PubMed: 7639978]
62. Limpakarnjanarat K, Mastro TD, Saisorn S, et al. HIV-1 and other sexually transmitted infections in a cohort of female sex workers in Chiang Rai, Thailand. Sexually transmitted infections. 1999; 75(1):30–5. [PubMed: 10448339]
63. Lurie P, Fernandes ME, Hughes V, et al. Socioeconomic status and risk of HIV-1, syphilis and hepatitis B infection among sex workers in Sao Paulo State, Brazil. Instituto Adolfo Lutz Study Group. AIDS. 1995; 9(Suppl 1):S31–7. [PubMed: 8561998]
64. Nelson KE, Eiumtrakul S, Celentano D, et al. The association of herpes simplex virus type 2 (HSV-2), Haemophilus ducreyi, and syphilis with HIV infection in young men in northern Thailand. J Acquir Immune Defic Syndr Hum Retrovirol. 1997; 16(4):293–300. [PubMed: 9402077]
65. Uribe-Salas F, Del Rio-Chiriboga C, Conde-Glez CJ, et al. Prevalence, incidence, and determinants of syphilis in female commercial sex workers in Mexico City. Sex Transm Dis. 1996; 23(2):120–6. [PubMed: 8919738]
66. Venegas VS, Madrid JP, Lorenzana I, Grillner L, Cosenza H, Bygdeman S. Human immunodeficiency virus infection and syphilis in Hondurian female prostitutes. Int J STD AIDS. 1991; 2(2):110–3. [PubMed: 2043701]
67••. Bibbins-Domingo K, Grossman DC, et al. U. S. Preventive Services Task Force. Screening for Syphilis Infection in Nonpregnant Adults and Adolescents: US Preventive Services Task Force Recommendation Statement. JAMA. 2016; 315(21):2321–7. The recommended guidelines for screening for syphilis infection in the US among certain groups. [PubMed: 27272583]
68. Zoni AC, Gonzalez MA, Sjogren HW. Syphilis in the most at-risk populations in Latin America and the Caribbean: a systematic review. Int J Infect Dis. 2013; 17(2):e84–92. [PubMed: 23063547]
69. Centers for Disease C, Prevention. Outbreak of syphilis among men who have sex with men--Southern California, 2000. MMWR Morb Mortal Wkly Rep. 2001; 50(7):117–20. [PubMed: 11393490]
70. Cowan S. Syphilis in Denmark-Outbreak among MSM in Copenhagen, 2003-2004. Euro Surveill. 2004; 9(12):25–7.
71. D'Souza G, Lee JH, Paffel JM. Outbreak of syphilis among men who have sex with men in Houston, Texas. Sex Transm Dis. 2003; 30(12):872–3. [PubMed: 14646631]
72. Emerson CR, Lynch A, Fox R, et al. The syphilis outbreak in Northern Ireland. Int J STD AIDS. 2007; 18(6):413–7. [PubMed: 17609034]
73. Giuliani M, Palamara G, Latini A, Maini A, Di Carlo A. Evidence of an outbreak of syphilis among men who have sex with men in Rome. Arch Dermatol. 2005; 141(1):100–1. [PubMed: 15655156]
74. Jayaraman GC, Read RR, Singh A. Characteristics of individuals with male-to-male and heterosexually acquired infectious syphilis during an outbreak in Calgary, Alberta, Canada. Sex Transm Dis. 2003; 30(4):315–9. [PubMed: 12671551]
75. Poulton M, Dean GL, Williams DI, Carter P, Iversen A, Fisher M. Surfing with spirochaetes: an ongoing syphilis outbreak in Brighton. Sexually transmitted infections. 2001; 77(5):319–21. [PubMed: 11588272]
76. Ruiz-Sancho A, Barreiro P, Castellares C, et al. Outbreak of syphilis, but not of acute hepatitis C, among HIV-infected homosexual men in Madrid. HIV Clin Trials. 2007; 8(2):98–101. [PubMed: 17507325]
77. Brignol S, Dourado I, Amorim LD, Kerr LR. Vulnerability in the context of HIV and syphilis infection in a population of men who have sex with men (MSM) in Salvador, Bahia State, Brazil. Cad Saude Publica. 2015; 31(5):1035–48. [PubMed: 26083178]

78. Johnston LG, Alami K, El Rhilani MH, et al. HIV, syphilis and sexual risk behaviours among men who have sex with men in Agadir and Marrakesh, Morocco. Sexually transmitted infections. 2013; 89(Suppl 3):iii45–8. [PubMed: 23620132]

79. Zhao Y, Luo T, Tucker JD, Wong WC. Risk Factors of HIV and Other Sexually Transmitted Infections in China: A Systematic Review of Reviews. PloS one. 2015; 10(10):e0140426. [PubMed: 26468650]

80. Joseph Davey DL, Shull HI, Billings JD, Wang D, Adachi K, Klausner JD. Prevalence of Curable Sexually Transmitted Infections in Pregnant Women in Low- and Middle-Income Countries From 2010 to 2015: A Systematic Review. Sex Transm Dis. 2016; 43(7):450–8. [PubMed: 27322048]

81. Chico RM, Mayaud P, Ariti C, Mabey D, Ronsmans C, Chandramohan D. Prevalence of malaria and sexually transmitted and reproductive tract infections in pregnancy in sub-Saharan Africa: a systematic review. JAMA. 2012; 307(19):2079–86. [PubMed: 22665107]

82. Bennani A, El-Kettani A, Hancali A, et al. The prevalence and incidence of active syphilis in women in Morocco, 1995-2016: Model-based estimation and implications for STI surveillance. PloS one. 2017; 12(8):e0181498. [PubMed: 28837558]

83. Bisseye C, Sanou M, Nagalo BM, et al. Epidemiology of syphilis in regional blood transfusion centres in Burkina Faso, West Africa. Pan Afr Med J. 2013; 16:69. [PubMed: 24711869]

84. Halatoko WA, Landoh DE, Saka B, et al. Prevalence of syphilis among female sex workers and their clients in Togo in 2011. BMC Public Health. 2017; 17(1):219. [PubMed: 28222772]

85. Sarkodie F, Hassall O, Owusu-Dabo E, et al. Syphilis screening practices in blood transfusion facilities in Ghana. Int J Infect Dis. 2016; 43:90–4. [PubMed: 26751240]

86. Ross MW, Nyoni J, Ahaneku HO, Mbwambo J, McClelland RS, McCurdy SA. High HIV seroprevalence, rectal STIs and risky sexual behaviour in men who have sex with men in Dar es Salaam and Tanga, Tanzania. BMJ Open. 2014; 4(8):e006175.

87. Norris AH, Loewenberg Weisband Y, Wiles M, Ickovics JR. Prevalence of sexually transmitted infections among Tanzanian migrants: a cross-sectional study. Int J STD AIDS. 2017; 28(10):991–1000. [PubMed: 28134004]

88. Endris M, Deressa T, Belyhun Y, Moges F. Seroprevalence of syphilis and human immunodeficiency virus infections among pregnant women who attend the University of Gondar teaching hospital, Northwest Ethiopia: a cross sectional study. BMC infectious diseases. 2015; 15:111. [PubMed: 25887081]

89. Abate M, Wolde T. Seroprevalence of Human Immunodeficiency Virus, Hepatitis B Virus, Hepatitis C Virus, and Syphilis among Blood Donors at Jigjiga Blood Bank, Eastern Ethiopia. Ethiop J Health Sci. 2016; 26(2):153–60. [PubMed: 27222628]

90. Shimelis T, Lemma K, Ambachew H, Tadesse E. Syphilis among people with HIV infection in southern Ethiopia: sero-prevalence and risk factors. BMC infectious diseases. 2015; 15:189. [PubMed: 25884178]

91. Mutagoma M, Nyirazinyoye L, Sebuhoro D, Riedel DJ, Ntaganira J. Syphilis and HIV prevalence and associated factors to their co-infection, hepatitis B and hepatitis C viruses prevalence among female sex workers in Rwanda. BMC infectious diseases. 2017; 17(1):525. [PubMed: 28754104]

92. Dionne-Odom J, Mbah R, Rembert NJ, et al. Hepatitis B, HIV, and Syphilis Seroprevalence in Pregnant Women and Blood Donors in Cameroon. Infectious diseases in obstetrics and gynecology. 2016; 2016:4359401. [PubMed: 27578957]

93. Manego RZ, Mombo-Ngoma G, Witte M, et al. Demography, maternal health and the epidemiology of malaria and other major infectious diseases in the rural department Tsamba-Magotsi, Ngounie Province, in central African Gabon. BMC Public Health. 2017; 17(1):130. [PubMed: 28129759]

94. Ginindza TG, Stefan CD, Tsoka-Gwegweni JM, et al. Prevalence and risk factors associated with sexually transmitted infections (STIs) among women of reproductive age in Swaziland. Infect Agent Cancer. 2017; 12:29. [PubMed: 28559923]

95. Ballah NJ, Kuonza LR, De Gita G, Musekiwa A, Williams S, Takuva S. Decline in syphilis seroprevalence among females of reproductive age in Northern Cape Province, South Africa, 2003-2012: utility of laboratory-based information. Int J STD AIDS. 2017; 28(6):564–72. [PubMed: 26924504]

96. Naidoo S, Wand H, Abbai NS, Ramjee G. High prevalence and incidence of sexually transmitted infections among women living in Kwazulu-Natal, South Africa. AIDS Res Ther. 2014; 11:31. [PubMed: 25243015]

97. Rebe K, Lewis D, Myer L, et al. A Cross Sectional Analysis of Gonococcal and Chlamydial Infections among Men-Who-Have-Sex-with-Men in Cape Town, South Africa. PloS one. 2015; 10(9):e0138315. [PubMed: 26418464]

98. Schwartz S, Lambert A, Phaswana-Mafuya N, et al. Engagement in the HIV care cascade and barriers to antiretroviral therapy uptake among female sex workers in Port Elizabeth, South Africa: findings from a respondent-driven sampling study. Sexually transmitted infections. 2017; 93(4): 290–6. [PubMed: 27888205]

99••. Australian Government Department of Health. Third National Sexually Transmissible Infections Strategy 2014–2017. 2014 Australia's Department of Health report on STIs.

100. Bright A, Dups J. Infectious and congenital syphilis notifications associated with an ongoing outbreak in northern Australia. Commun Dis Intell Q Rep. 2016; 40(1):E7–10. [PubMed: 27080030]

101. Lucky TT, Seed CR, Keller A, et al. Trends in transfusion-transmissible infections among Australian blood donors from 2005 to 2010. Transfusion. 2013; 53(11):2751–62. [PubMed: 23461827]

102•. Zhang X, Hou F, Li X, Zhou L, Liu Y, Zhang T. Study of surveillance data for class B notifiable disease in China from 2005 to 2014. Int J Infect Dis. 2016; 48:7–13. A report using China's surveillance data for notifiable diseases. [PubMed: 27094249]

103. Yang S, Jiao D, Liu C, et al. Seroprevalence of human immunodeficiency virus, hepatitis B and C viruses, and Treponema pallidum infections among blood donors at Shiyan, Central China. BMC infectious diseases. 2016; 16(1):531. [PubMed: 27716251]

104. Chen Y, Tang W, Chen L, et al. Changing Epidemic of HIV and Syphilis Among Resident and Migrant Men Who Have Sex with Men in Jiangsu, China. Sci Rep. 2017; 7(1):9478. [PubMed: 28842553]

105. Hu J, Gu X, Tao X, et al. Prevalence and Trends of HIV, Syphilis, and HCV in Migrant and Resident Men Who Have Sex with Men in Shandong, China: Results from a Serial Cross-Sectional Study. PloS one. 2017; 12(1):e0170443. [PubMed: 28103295]

106. Chen Y, Abraham Bussell S, Shen Z, et al. Declining Inconsistent Condom Use but Increasing HIV and Syphilis Prevalence Among Older Male Clients of Female Sex Workers: Analysis From Sentinel Surveillance Sites (2010-2015), Guangxi, China. Medicine (Baltimore). 2016; 95(22):e3726. [PubMed: 27258500]

107. Zou X, Ling L, Zhang L. Trends and risk factors for HIV, HCV and syphilis seroconversion among drug users in a methadone maintenance treatment programme in China: a 7-year retrospective cohort study. BMJ Open. 2015; 5(8):e008162.

108. Sun Y, Guo W, Li G, He S, Lu H. Increased synthetic drug abuse and trends in HIV and syphilis prevalence among female drug users from 2010-2014 from Beijing, China. Int J STD AIDS. 2017 956462417715174.

109••. European Centre for Disease Prevention and Control. Sexually transmitted infections in Europe 2013 Stockholm: ECDC. 2015 Europe's Department of Health report on STIs.

110. Tsankova G, Todorova TT, Kostadinova T, Ivanova L, Ermenlieva N. Seroprevalence of Syphilis among Pregnant Women in the Varna Region (Bulgaria). Acta Dermatovenerol Croat. 2016; 24(4):288–90. [PubMed: 28128080]

111. Bozicevic I, Lepej SZ, Rode OD, et al. Prevalence of HIV and sexually transmitted infections and patterns of recent HIV testing among men who have sex with men in Zagreb, Croatia. Sexually transmitted infections. 2012; 88(7):539–44. [PubMed: 22628664]

112. Thorsteinsson K, Ladelund S, Storgaard M, et al. Sexually transmitted infections and use of contraceptives in women living with HIV in Denmark - the SHADE cohort. BMC infectious diseases. 2016; 16:81. [PubMed: 26880101]

113. Legoupil C, Peltier A, Henry Kagan V, et al. Out-of-Hospital screening for HIV, HBV, HCV and Syphilis in a vulnerable population, a public health challenge. AIDS care. 2017; 29(6):686–8. [PubMed: 27626811]

114. Amelot F, Picot E, Meusy A, Rousseau C, Brun M, Guillot B. Syphilis in Montpellier, France, from 2002 to 2011: Survey in a free hospital screening centre for venereal disease and in the dermatology unit of a regional public hospital. Ann Dermatol Venereol. 2015; 142(12):742–50. [PubMed: 26362133]

115. Champenois K, Cousien A, Ndiaye B, et al. Risk factors for syphilis infection in men who have sex with men: results of a case-control study in Lille, France. Sexually transmitted infections. 2013; 89(2):128–32. [PubMed: 22679099]

116. Corsenac P, Noel M, Rouchon B, Hoy D, Roth A. Prevalence and sociodemographic risk factors of chlamydia, gonorrhoea and syphilis: a national multicentre STI survey in New Caledonia, 2012. BMJ Open. 2015; 5(9):e007691.

117•. Jansen K, Schmidt AJ, Drewes J, Bremer V, Marcus U. Increased incidence of syphilis in men who have sex with men and risk management strategies, Germany, 2015. Euro Surveill. 2016; 21(43) A report showing increased incidence of syphilis among MSM in Germany.

118. Jansen K, Thamm M, Bock CT, et al. High Prevalence and High Incidence of Coinfection with Hepatitis B, Hepatitis C, and Syphilis and Low Rate of Effective Vaccination against Hepatitis B in HIV-Positive Men Who Have Sex with Men with Known Date of HIV Seroconversion in Germany. PloS one. 2015; 10(11):e0142515. [PubMed: 26555244]

119. Fuchs W, Kreuter A, Hellmich M, et al. Asymptomatic anal sexually transmitted infections in HIV-positive men attending anal cancer screening. Br J Dermatol. 2016; 174(4):831–8. [PubMed: 26577338]

120. Marcus U, Ort J, Grenz M, Eckstein K, Wirtz K, Wille A. Risk factors for HIV and STI diagnosis in a community-based HIV/STI testing and counselling site for men having sex with men (MSM) in a large German city in 2011-2012. BMC infectious diseases. 2015; 15:14. [PubMed: 25582975]

121. Bremer V, Haar K, Gassowski M, Hamouda O, Nielsen S. STI tests and proportion of positive tests in female sex workers attending local public health departments in Germany in 2010/11. BMC Public Health. 2016; 16(1):1175. [PubMed: 27871264]

122. Jablonka A, Solbach P, Nothdorft S, Hampel A, Schmidt RE, Behrens GM. Low seroprevalence of syphilis and HIV in refugees and asylum seekers in Germany in 2015. Dtsch Med Wochenschr. 2016; 141(14):e128–32. [PubMed: 27404938]

123. Kanelleas A, Stefanaki C, Stefanaki I, et al. Primary syphilis in HIV-negative patients is on the rise in Greece: epidemiological data for the period 2005-2012 from a tertiary referral centre in Athens, Greece. J Eur Acad Dermatol Venereol. 2015; 29(5):981–4. [PubMed: 25327583]

124. Tsachouridou O, Skoura L, Christaki E, et al. Syphilis on the rise: A prolonged syphilis outbreak among HIV-infected patients in Northern Greece. Germs. 2016; 6(3):83–90. [PubMed: 27622160]

125. Albertsen N, Mulvad G, Pedersen ML. Incidence of syphilis in Greenland 2010-2014: the beginning of a new epidemic? Int J Circumpolar Health. 2015; 74:28378.

126. McGettrick P, Ferguson W, Jackson V, et al. Syphilis serology in pregnancy: an eight-year study (2005-2012) in a large teaching maternity hospital in Dublin, Ireland. Int J STD AIDS. 2016; 27(3):226–30. [PubMed: 25829517]

127. Padovese V, Egidi AM, Melillo TF, et al. Prevalence of latent tuberculosis, syphilis, hepatitis B and C among asylum seekers in Malta. J Public Health (Oxf). 2014; 36(1):22–7. [PubMed: 23559596]

128. Zohrabyan L, Johnston LG, Scutelniciuc O, et al. Determinants of HIV infection among female sex workers in two cities in the Republic of Moldova: the role of injection drug use and sexual risk. AIDS Behav. 2013; 17(8):2588–96. [PubMed: 23539186]

129. de Coul EL, Warning TD, Koedijk FD. Dutch STIc. Sexual behaviour and sexually transmitted infections in sexually transmitted infection clinic attendees in the Netherlands, 2007-2011. Int J STD AIDS. 2014; 25(1):40–51. [PubMed: 23970630]

130. van Aar F, den Daas C, van der Sande MAB, Soetens LC, de Vries HJC, van Benthem BHB. Outbreaks of syphilis among men who have sex with men attending STI clinics between 2007 and 2015 in the Netherlands: a space-time clustering study. Sexually transmitted infections. 2017; 93(6):390–5. [PubMed: 27986969]

131. Slot E, Janssen MP, Marijt-van der Kreek T, Zaaijer HL, van de Laar TJ. Two decades of risk factors and transfusion-transmissible infections in Dutch blood donors. Transfusion. 2016; 56(1): 203–14. [PubMed: 26355711]

132. Fournet N, Koedijk FD, van Leeuwen AP, van Rooijen MS, van der Sande MA, van Veen MG. Young male sex workers are at high risk for sexually transmitted infections, a cross-sectional study from Dutch STI clinics, the Netherlands, 2006-2012. BMC infectious diseases. 2016; 16:63. [PubMed: 26847196]

133. Verscheijden MMA, Woestenberg PJ, Gotz HM, van Veen MG, Koedijk FDH, van Benthem BHB. Sexually transmitted infections among female sex workers tested at STI clinics in the Netherlands, 2006-2013. Emerging themes in epidemiology. 2015; 12:12. [PubMed: 26322117]

134. Jakopanec I, Grjibovski AM, Nilsen O, Blystad H, Aavitsland P. Trends in HIV infection surveillance data among men who have sex with men in Norway, 1995-2011. BMC Public Health. 2013; 13:144. [PubMed: 23414557]

135. Serwin AB, Unemo M. Syphilis in females in Bialystok, Poland, 2000-2015. Przegl Epidemiol. 2016; 70(2):273–80. [PubMed: 27837577]

136. Serwin AB, Koper M, Unemo M. Clinical and epidemiological characteristics of males with syphilis in Bialystok, Poland in 2008-2013. Przegl Epidemiol. 2015; 69(1):41–5. 143–6. [PubMed: 25862446]

137. Majewski S, Rudnicka I. Sexually transmitted diseases in Poland in 2011. Przegl Epidemiol. 2013; 67(2):283–6. 379–81. [PubMed: 24040734]

138. Lopes L, Ferro-Rodrigues R, Llobet S, Lito L, Borges-Costa J. Syphilis: Prevalence in a Hospital in Lisbon. Acta Med Port. 2016; 29(1):52–5. [PubMed: 26926899]

139. Bjekic M, Vlajinac H, Sipetic-Grujicic S. Characteristics of gonorrhea and syphilis cases among the Roma ethnic group in Belgrade, Serbia. Braz J Infect Dis. 2016; 20(4):349–53. [PubMed: 27280790]

140. Marti-Pastor M, Garcia de Olalla P, Barbera MJ, et al. Epidemiology of infections by HIV, Syphilis, Gonorrhea and Lymphogranuloma Venereum in Barcelona City: a population-based incidence study. BMC Public Health. 2015; 15:1015. [PubMed: 26438040]

141. Svecova D, Part M, Luha J. Increasing trend in syphilis. Bratisl Lek Listy. 2015; 116(10):596–600. [PubMed: 26531870]

142. Azbel L, Wickersham JA, Grishaev Y, Dvoryak S, Altice FL. Burden of infectious diseases, substance use disorders, and mental illness among Ukrainian prisoners transitioning to the community. PloS one. 2013; 8(3):e59643. [PubMed: 23527238]

143•. Mohammed H, Mitchell H, Sile B, Duffell S, Nardone A, Hughes G. Increase in Sexually Transmitted Infections among Men Who Have Sex with Men, England, 2014. Emerg Infect Dis. 2016; 22(1):88–91. A report showing increased incidence of syphilis among MSM in England. [PubMed: 26689861]

144•. Malek R, Mitchell H, Furegato M, et al. Contribution of transmission in HIV-positive men who have sex with men to evolving epidemics of sexually transmitted infections in England: an analysis using multiple data sources, 2009-2013. Euro Surveill. 2015; 20(15) An analysis showing increased incidence of syphilis among HIV-infected MSM in England.

145. Mayor S. Syphilis and gonorrhoea increase sharply in England. Bmj. 2015; 350:h3457. [PubMed: 26116688]

146. Simms I, Wallace L, Thomas DR, et al. Recent outbreaks of infectious syphilis, United Kingdom, January 2012 to April 2014. Euro Surveill. 2014; 19(24)

147. Thomas DR, Williams CJ, Andrady U, et al. Outbreak of syphilis in men who have sex with men living in rural North Wales (UK) associated with the use of social media. Sexually transmitted infections. 2016; 92(5):359–64. [PubMed: 27147613]

148. Petersen J, Gibin M, Sile B, Simms I. Identifying and interpreting spatiotemporal variation in diagnoses of infectious syphilis among men, England: 2009 to 2013. Sexually transmitted infections. 2016; 92(5):380–6. [PubMed: 27147614]

149. Mitchell H, Furegato M, Hughes G, Field N, Nardone A. What are the characteristics of, and clinical outcomes in men who have sex with men prescribed HIV postexposure prophylaxis

following sexual exposure (PEPSE) at sexual health clinics in England? Sexually transmitted infections. 2017; 93(3):207–13. [PubMed: 27884964]

150. Mc Grath-Lone L, Marsh K, Hughes G, Ward H. The sexual health of female sex workers compared with other women in England: analysis of cross-sectional data from genitourinary medicine clinics. Sexually transmitted infections. 2014; 90(4):344–50. [PubMed: 24493858]
151. Simms I, Tookey PA, Goh BT, et al. The incidence of congenital syphilis in the United Kingdom: February 2010 to January 2015. BJOG. 2017; 124(1):72–7. [PubMed: 26931054]
152. Kojima N, Park H, Konda KA, et al. The PICASSO Cohort: baseline characteristics of a cohort of men who have sex with men and male-to-female transgender women at high risk for syphilis infection in Lima, Peru. BMC infectious diseases. 2017; 17(1):255. [PubMed: 28399798]
153. Cunha CB, Friedman RK, de Boni RB, et al. Chlamydia trachomatis, Neisseria gonorrhoeae and syphilis among men who have sex with men in Brazil. BMC Public Health. 2015; 15:686. [PubMed: 26195002]
154. Bissio E, Cisneros V, Lopardo GD, Cassetti LI. Very high incidence of syphilis in HIV-infected men who have sex with men in Buenos Aires city: a retrospective cohort study. Sexually transmitted infections. 2017; 93(5):323–6. [PubMed: 27856515]
155. Centers for Disease Control and Prevention. [27 Oct] Syphilis. Available at: https://www.cdc.gov/std/stats16/syphilis.htm
156•. Solomon MM, Mayer KH. Evolution of the syphilis epidemic among men who have sex with men. Sexual health. 2015; 12(2):96–102. A review of syphilis among MSM. [PubMed: 25514173]
157. Adams EJ, Garcia PJ, Garnett GP, Edmunds WJ, Holmes KK. The cost-effectiveness of syndromic management in pharmacies in Lima, Peru. Sex Transm Dis. 2003; 30(5):379–87. [PubMed: 12916127]
158. Sanchez J, Volquez C, Totten PA, et al. The etiology and management of genital ulcers in the Dominican Republic and Peru. Sex Transm Dis. 2002; 29(10):559–67. [PubMed: 12370522]
159. Tsai CH, Lee TC, Chang HL, Tang LH, Chiang CC, Chen KT. The cost-effectiveness of syndromic management for male sexually transmitted disease patients with urethral discharge symptoms and genital ulcer disease in Taiwan. Sexually transmitted infections. 2008; 84(5):400–4. [PubMed: 18426845]
160. Clark JL, Lescano AG, Konda KA, et al. Syndromic management and STI control in urban Peru. PloS one. 2009; 4(9):e7201. [PubMed: 19779620]
161. Tucker JD, Bien CH, Peeling RW. Point-of-care testing for sexually transmitted infections: recent advances and implications for disease control. Curr Opin Infect Dis. 2013; 26(1):73–9. [PubMed: 23242343]
162. Leon SR, Ramos LB, Vargas SK, et al. Laboratory Evaluation of a Dual-Path Platform Assay for Rapid Point-of-Care HIV and Syphilis Testing. J Clin Microbiol. 2016; 54(2):492–4. [PubMed: 26659215]
163. Gliddon HD, Peeling RW, Kamb ML, Toskin I, Wi TE, Taylor MM. A systematic review and meta-analysis of studies evaluating the performance and operational characteristics of dual point-of-care tests for HIV and syphilis. Sexually transmitted infections. 2017
164. Bristow CC, Leon SR, Huang E, et al. Field evaluation of a dual rapid diagnostic test for HIV infection and syphilis in Lima, Peru. Sexually transmitted infections. 2016; 92(3):182–5. [PubMed: 26670914]
165. Bristow CC, Leon SR, Ramos LB, et al. Laboratory evaluation of a dual rapid immunodiagnostic test for HIV and syphilis infection. J Clin Microbiol. 2015; 53(1):311–3. [PubMed: 25378568]
166. Herbst de Cortina S, Bristow CC, Vargas SK, et al. Laboratory Evaluation of a Point-of-Care Downward-Flow Assay for Simultaneous Detection of Antibodies to Treponema pallidum and Human Immunodeficiency Virus. J Clin Microbiol. 2016; 54(7):1922–4. [PubMed: 27147725]
167. World Health Organization. WHO Information Note on the Use of Dual HIV/Syphilis Rapid Diagnostic Tests (RDT). 2017
168. Marks M, Mabey DC. The introduction of syphilis point of care tests in resource limited settings. Expert Rev Mol Diagn. 2017; 17(4):321–5. [PubMed: 28266230]

169. Klausner JD. The Evidence That Increased Syphilis Testing Controls Syphilis Is Compelling: What Is Needed to Act? Clin Infect Dis. 2017; 65(3):396–7. [PubMed: 28419214]

170. Gulland A. Number of cases of syphilis continue to rise. Bmj. 2017; 357:j2807. [PubMed: 28600280]

171. McCarthy M. Syphilis rate rises in the US. Bmj. 2014; 349:g7756. [PubMed: 25527470]

172. Chow EPF, Callander D, Fairley CK, et al. Increased Syphilis Testing of Men Who Have Sex With Men: Greater Detection of Asymptomatic Early Syphilis and Relative Reduction in Secondary Syphilis. Clin Infect Dis. 2017; 65(3):389–95. [PubMed: 28419198]

173. Peterman TA, Su J, Bernstein KT, Weinstock H. Syphilis in the United States: on the rise? Expert Rev Anti Infect Ther. 2015; 13(2):161–8. [PubMed: 25487961]

174•. Stamm LV. Syphilis: Re-emergence of an old foe. Microb Cell. 2016; 3(9):363–70. A review of syphilis among MSM. [PubMed: 28357375]

175. World Health Organization. Organization WH. Geneva, Switzerland: World Health Organization; 2017. Report of the 21st WHO Expert Committee on the Selection and Use of Essential Medicines.

176. U.S. Food and Drug Administration. [20 Oct] Current and Resolved Drug Shortages and Discontinuations Reported to FDA. Available at: https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=PenicillinGProcaineInjection&st=c&tab=tabs-1

177. Centers for Disease Control and Prevention. [20 Oct] Procaine Penicillin G Shortage. Available at: https://www.cdc.gov/std/treatment/drugnotices/procaine-peng.htm

178. World Health Organization. Technical consultation on preventing and managing global stock outs of medicines. Geneva, Switzerland: World Health Organization; 2015.

179. Taylor MM, Zhang X, Nurse-Findlay S, Hedman L, Kiarie J. The amount of penicillin needed to prevent mother-to-child transmission of syphilis. Bull World Health Organ. 2016; 94(8):559–A. [PubMed: 27516630]

180. Taylor MM, Nurse-Findlay S, Zhang X, et al. Estimating Benzathine Penicillin Need for the Treatment of Pregnant Women Diagnosed with Syphilis during Antenatal Care in High-Morbidity Countries. PloS one. 2016; 11(7):e0159483. [PubMed: 27434236]

181. Stamm LV. Global challenge of antibiotic-resistant Treponema pallidum. Antimicrob Agents Chemother. 2010; 54(2):583–9. [PubMed: 19805553]

182. Stamm LV. Syphilis: antibiotic treatment and resistance. Epidemiol Infect. 2015; 143(8):1567–74. [PubMed: 25358292]

183. Li Z, Hou J, Zheng R, et al. Two mutations associated with macrolide resistance in Treponema pallidum in Shandong, China. J Clin Microbiol. 2013; 51(12):4270–1. [PubMed: 24048540]

184. Katz KA, Klausner JD. Azithromycin resistance in Treponema pallidum. Curr Opin Infect Dis. 2008; 21(1):83–91. [PubMed: 18192791]

185. Grimes M, Sahi SK, Godornes BC, et al. Two mutations associated with macrolide resistance in Treponema pallidum: increasing prevalence and correlation with molecular strain type in Seattle, Washington. Sex Transm Dis. 2012; 39(12):954–8. [PubMed: 23191949]

186. A. G. Prevalence Workgroup. Prevalence of the 23S rRNA A2058G point mutation and molecular subtypes in Treponema pallidum in the United States, 2007 to 2009. Sex Transm Dis. 2012; 39(10):794–8. [PubMed: 23001267]

187. Chen XS, Yin YP, Wei WH, et al. High prevalence of azithromycin resistance to Treponema pallidum in geographically different areas in China. Clin Microbiol Infect. 2013; 19(10):975–9. [PubMed: 23231450]

188. Muldoon EG, Walsh A, Crowley B, Mulcahy F. Treponema pallidum azithromycin resistance in Dublin, Ireland. Sex Transm Dis. 2012; 39(10):784–6. [PubMed: 23001265]

189. Read P, Jeoffreys N, Tagg K, Guy RJ, Gilbert GL, Donovan B. Azithromycin-resistant syphilis-causing strains in Sydney, Australia: prevalence and risk factors. J Clin Microbiol. 2014; 52(8):2776–81. [PubMed: 24850356]

190. Muller EE, Paz-Bailey G, Lewis DA. Macrolide resistance testing and molecular subtyping of Treponema pallidum strains from southern Africa. Sexually transmitted infections. 2012; 88(6):470–4. [PubMed: 22611234]

191. Van Damme K, Behets F, Ravelomanana N, et al. Evaluation of azithromycin resistance in Treponema pallidum specimens from Madagascar. Sex Transm Dis. 2009; 36(12):775–6. [PubMed: 19901863]

192. Wu BR, Yang CJ, Tsai MS, et al. Multicentre surveillance of prevalence of the 23S rRNA A2058G and A2059G point mutations and molecular subtypes of Treponema pallidum in Taiwan, 2009-2013. Clin Microbiol Infect. 2014; 20(8):802–7. [PubMed: 24438059]

193. Wu H, Chang SY, Lee NY, et al. Evaluation of macrolide resistance and enhanced molecular typing of Treponema pallidum in patients with syphilis in Taiwan: a prospective multicenter study. J Clin Microbiol. 2012; 50(7):2299–304. [PubMed: 22518868]

194. Bolan RK, Beymer MR, Weiss RE, Flynn RP, Leibowitz AA, Klausner JD. Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: a randomized, controlled pilot study. Sex Transm Dis. 2015; 42(2):98–103. [PubMed: 25585069]

195. Molina JM, Charreau I, Chidiac C, Pialoux G, Cua E, Delaugerre C, Capitant C, Rojas-Castro D, Meyer L. ON DEMAND POST EXPOSURE PROPHYLAXIS WITH DOXYCYCLINE FOR MSM ENROLLED IN A PREP TRIAL. Conference on Retroviruses and Opportunistic Infections; Seattle, Washington. 2017.

196. Steen R, Chersich M, Gerbase A, et al. Periodic presumptive treatment of curable sexually transmitted infections among sex workers: a systematic review. AIDS. 2012; 26(4):437–45. [PubMed: 22095197]

197. Cameron CE, Lukehart SA. Current status of syphilis vaccine development: need, challenges, prospects. Vaccine. 2014; 32(14):1602–9. [PubMed: 24135571]

198. Lithgow KV, Cameron CE. Vaccine development for syphilis. Expert Rev Vaccines. 2017; 16(1): 37–44. [PubMed: 27328030]

199. Lithgow KV, Hof R, Wetherell C, Phillips D, Houston S, Cameron CE. A defined syphilis vaccine candidate inhibits dissemination of Treponema pallidum subspecies pallidum. Nat Commun. 2017; 8:14273. [PubMed: 28145405]

200. The State Journal-Register. GateHouse Medi; Springfield, IL: Feb 11, 2017 Our View: Budget options would help Illinois determine best path forward.

201. Roberts WC. Facts and ideas from anywhere. Proc (Bayl Univ Med Cent). 2004; 17(1):89–94. [PubMed: 16200093]

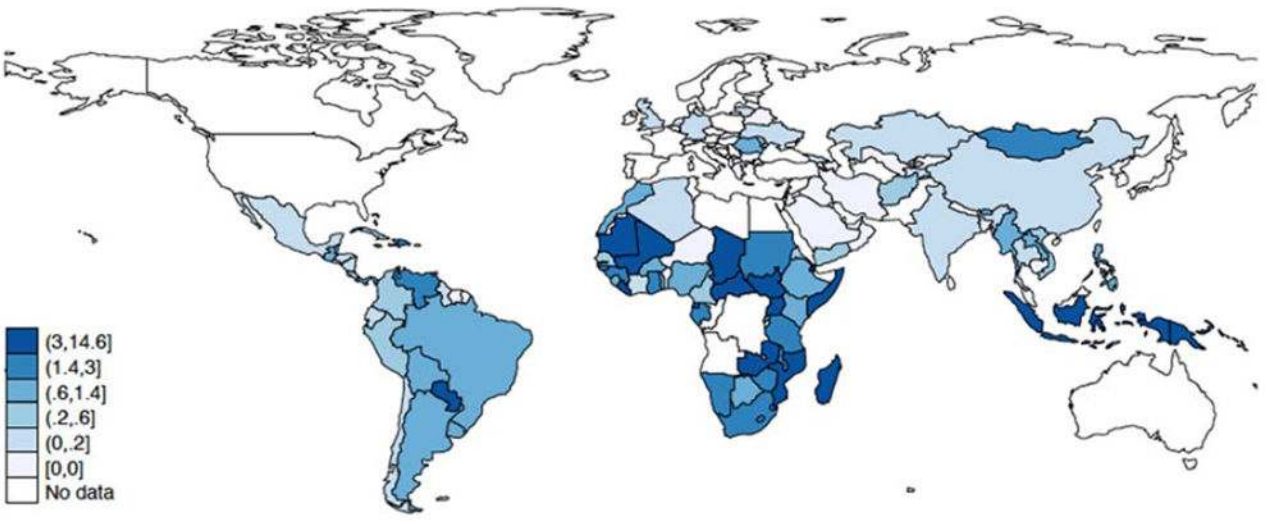
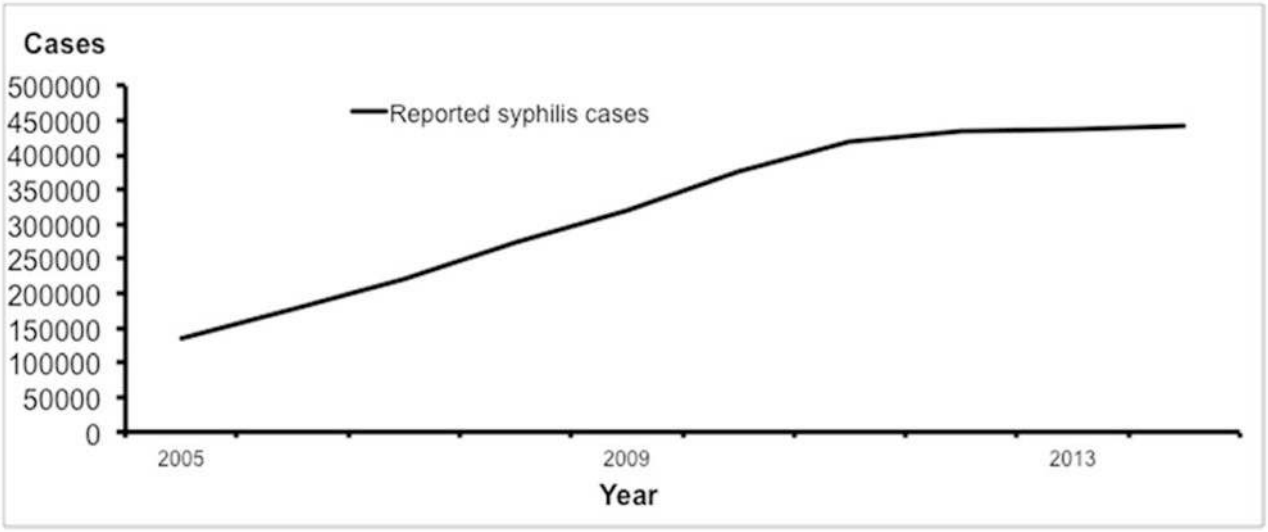
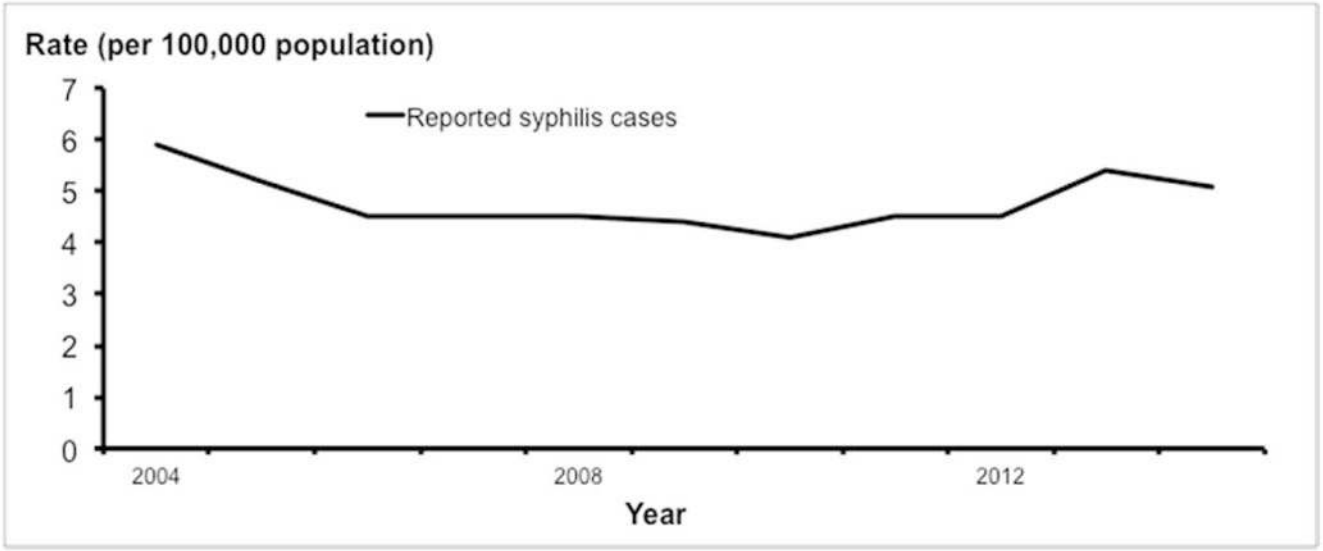


Figure 1.
Geographic distribution of syphilis prevalence at first antenatal care visit, 2015





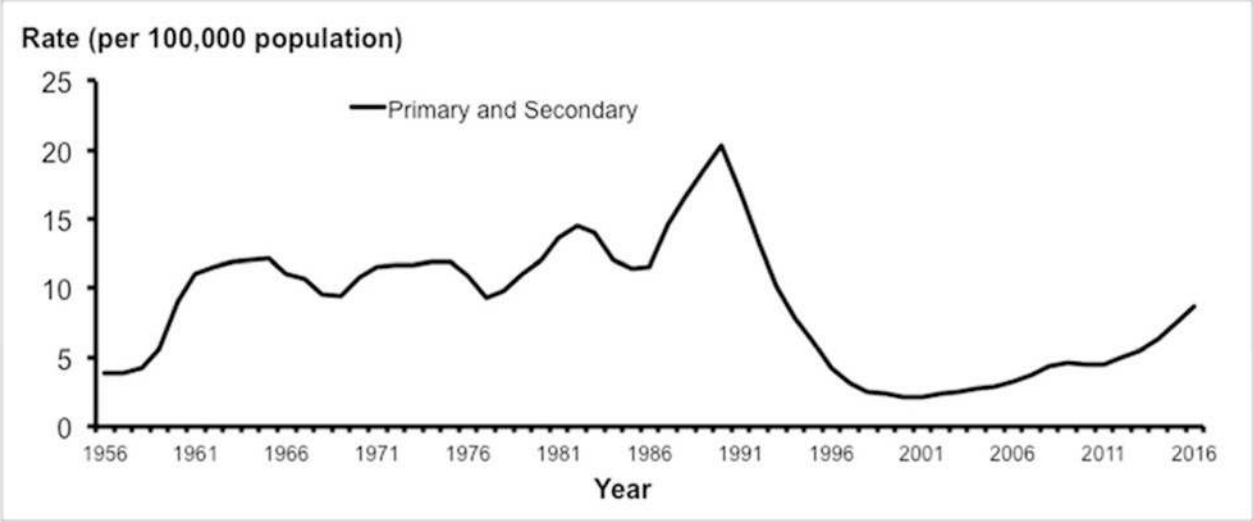


Figure 2.

a. Reported syphilis cases in China from 2005 to 2014.

b. Reported syphilis cases in Europe from 2004 to 2014.

c. Primary and secondary syphilis cases in the United States from 1956 to 2016.

Table 1

Select aggregate measures of syphilis testing, treatment, and disease burden by country income status

Country Income			
High	**High Middle**	**Low Middle**	**Low**
Antenatal care attendees tested for syphilis at first antenatal care visit (median [%], Interquartile Range [IQR])			
99.9 (93.25, 100)	82.7 (54, 99.5)	67.7 (42.7, 94.5)	29.4 (7.55, 53.9)
Antenatal care attendees positive for syphilis (median [%], IQR)			
0.1 (0, 0.2)	0.6 (0.1, 1.65)	0.9 (0.1, 2.4)	1.9 (0.6, 3.9)
Antenatal care attendees positive for syphilis who received treatment (median [%], IQR)			
100 (89.45, 100)	91.7 (67.9, 100)	88.4 (60.3, 100)	88.1 (52.9, 100)
Congenital syphilis rate per 100,000 cases (median, IQR)			
0.3 (0, 3.45)	4.6 (0, 87.9)	4.85 (0.2, 26.4)	417.5 (-)
Sex workers with active syphilis (median [%], IQR)			
0.85 (0.45, 6.3)	3.2 (1.4, 9.15)	4.1 (1, 9.6)	4.3 (1.3, 19.6)
Men who have sex with men with active syphilis (median [%], IQR)			
7 (3.8, 9.6)	6 (2, 13.7)	3.8 (1.2, 5.5)	3.9 (1.1, 9.7)

From data from the World Health Organization and the World Bank [11, 57].