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An Update on the Global Epidemiology of Syphilis

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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 countries.

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 countries.

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.

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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 through 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 coinfecting 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 Province, 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 Shiyuan 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 throughout 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 had 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 Caledonia¹ 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].

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¹New 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 asymptomatic 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 ethnically 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].”

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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].