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Context appropriate interventions to prevent syphilis: a narrative review

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Abstract

Background: The success of an intervention to prevent syphilis will depend on the context and the goal of the intervention. To help programs choose interventions, we reviewed major changes in context and types of interventions that may be effective.

Methods: We reviewed the literature on the changing context of syphilis in the United States and interventions to prevent syphilis, focusing on papers that included evidence of effectiveness.

Results: Populations acquiring syphilis are constantly changing. Currently, incidence is very high among men who have sex with men. Among adults, late disease caused by syphilis has become rare. Congenital syphilis incidence has been low but is increasing, and morbidity and mortality remain high when babies are infected. Congenital syphilis now causes more deaths than syphilis among adults.

Routine screening of MSM can identify and treat infections before they progress to disease (secondary prevention). Screening rates are highest when done as part of routine standing orders. Partner notification effectiveness has decreased, partly because many partners are anonymous. Most congenital syphilis can be prevented by screening pregnant women; it has been eliminated in areas where intense primary prevention efforts eliminated syphilis among women.

Conclusion: So far, no program has stopped the increasing rates of infection among MSM, but secondary prevention efforts have prevented most disability. Congenital syphilis is increasing, and can be decreased by screening pregnant women and stopped by intensive efforts to prevent infection among women.

Brief summary:

Serious complications of syphilis are rare among adults, but common when babies are infected. Secondary prevention can prevent most illness among adults. Primary prevention is needed to prevent congenital syphilis.

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Keywords

syphilis; congenital syphilis; control; screening; partner notification; history; surveillance

Introduction

Syphilis has changed. There have been changes in the disease, persons at risk, and factors that influence transmission. Many of these changes alter the effectiveness of interventions that prevention programs may be considering. The success of those interventions will depend on the context. Central to the present context in the United States is consideration of the consequences of syphilis, namely the low frequency of complications among adults and the high frequency of complications among developing infants. This review describes the changing context, and the most successful interventions for these epidemics. We focused on the context in the United States, though we also include relevant studies done elsewhere. Every context is different, so the response to syphilis should begin by assessing the context, deciding on a goal, and implementing the interventions that are most promising. This should be immediately followed by monitoring to assess effectiveness, identifying more promising alternatives, and repeating the process.(Text box 1)

Context

Adults with syphilis

The severity of disease caused by Treponema pallidum has changed. In 1900, 28% of adults developed serious complications (often 10–30 years after infection) and the case-fatality rate was 10% within 40 years.[1] Deaths due to syphilis fell from 20,000 per year in the 1930's to 40 per year since 2000.[2, 3] Disease rates have also decreased, but current levels have not been accurately quantified because surveillance focuses on rates of infection, not complications. Therefore, descriptions of syphilis continue to cite old rates and note that they have since decreased.[4] In the early 1900's, over 10% of patients with syphilis developed cardiovascular syphilis.[1] Between 1927 and 1937, 6.9% (1,040) of the 15,000 autopsies at Philadelphia General Hospital had evidence of cardiovascular syphilis.[5] Since 1998, 2–4 patients per year have had syphilitic aortic aneurysms resected at Baylor University Medical Center.[6] The likelihood of symptomatic neurosyphilis is also much lower than it was during the pre-penicillin era. It is now about 1.2%–1.7% with 0.5% still having some degree of disability 6 months after treatment.[7, 8] Recent reports of blindness due to ocular syphilis raised concerns that there might be a more aggressive strain of *Treponema pallidum*, but subsequent studies have found multiple strains were associated with ocular syphilis.[9] Furthermore, the likelihood of early ocular complications among infected persons was similar to past reports (1.5%)[10] suggesting that the increased reporting was due to increased recognition and increases in syphilis, not a change in pathogenesis. Syphilis can still cause disability among adults, but it is rare.

The characteristics of adults at highest risk for syphilis are constantly changing. Syphilis was widespread in the pre-penicillin era. For example, the incidence of early syphilis was 1.8% in the U.S. Army at home in 1914.[11] Rates fell dramatically after penicillin became

available in the late 1940's.[12] Epidemics associated with crack cocaine swept across the United States, peaking in 1990,[13–15] and rates of primary and secondary syphilis among blacks reached 62 times the rates among whites.[12] Now the black:white rate ratio is less than 5.[16] Other characteristics of groups at highest risk have changed. The age of men at highest risk changed from 35–39 in 2003 to 25–29 in 2016.[16, 17] Information on sex-of-sex-partners was not collected nationally for syphilis until 2005.[18] Estimates based on the male:female rate ratio show men who have sex with men (MSM) in the United States were at extremely high risk in 1981.[19, 20] Rates among MSM fell when many were dying from AIDS and by the 1990s almost no MSM got syphilis.[20] Now estimated rates among MSM are as high as ever (about 180 times the rates among women) (Figure 1). Rates among women were as high as 17 per 100,000 in 1990,[12] and are now lower at 1.9 per 100,000, though they have doubled since 2012.[16]

Congenital syphilis

In 1933 there were 1,639 infant deaths attributed to syphilis.[2] These did not include stillbirths, later deaths, or other serious complications. Major changes in case definitions (that increased sensitivity but decreased specificity) have made it difficult to monitor changes in congenital syphilis rates,[21, 22] though they have clearly fallen as rates of infection among women have fallen. However, when it does occur, congenital syphilis continues to have the same devastating consequences for babies that it did in the pre-penicillin era. Untreated syphilis results in a 52% absolute increase in adverse outcomes of pregnancy, including absolute increases in: fetal loss or stillbirth (21%) (26% among women with untreated syphilis compared to 5% among women without syphilis), neonatal death (9%), premature or low birth weight infant (6%), and other infants with signs or symptoms of syphilis (15%).[23] Trends in congenital syphilis closely mirror syphilis trends among women (Figure 2). Between 2012 and 2016, primary and secondary syphilis cases among women in the United States increased by 109% and congenital syphilis cases increased by 88% to 628 cases.[16] Most of this increase came from California where cases among women increased by 541% (from 116 to 744) and congenital cases increased by 489%, from 35 to 206.[16] Despite the low number of congenital infections, the impact of congenital syphilis and contribution to syphilis-related disease is high. The case-fatality ratio has remained at 6.5% during 1992–2013.[24, 25] Among the 458 cases of congenital syphilis reported in 2014, 33 (7.2%) ended in stillbirth or neonatal death.[26] In 2016, the number of syphilitic stillbirths exceeded the average number of deaths attributed to syphilis among adults between 2000 and 2014.[3, 16]

Goal

The goal of an intervention could be to prevent infection (primary prevention), or to prevent disease in the infected person (secondary prevention), or both. Sexual transmission occurs from lesions (that may not be apparent), during primary and secondary syphilis, so stopping sexual transmission requires treating (or preventing) early infections.[4, 27] Preventing disease in adults does not require the same urgency as preventing transmission, though recently complications of syphilis in adults (i.e., neurosyphilis and ocular syphilis) have usually occurred within a few years of infection. Preventing disease due to congenital syphilis requires urgent detection and treatment because complications can occur very soon after

infection. Congenital infection can manifest early, as stillbirth, premature birth, and neonatal death; or late, if asymptomatic babies are not treated. Therefore, in high prevalence areas, preventing complications of congenital syphilis requires three screening tests: one early in pregnancy to prevent stillbirths; another at 28–32 weeks to detect infections acquired later during pregnancy while they can still be easily treated; and a third at delivery to detect infections acquired after both earlier tests.[28]

Interventions

Technology is changing both opportunities to transmit syphilis, and opportunities to intervene. Mobile apps facilitate anonymous sex which limits the ability to find and treat partners.[29, 30] Long-distance trips for parties or sex-oriented vacations are increasingly common[31] and limit the ability to control disease with solely local campaigns. However, new technology also allows health departments to efficiently locate partners via email, text messages, or Facebook.[32, 33] Many health departments maintain websites that allow efficient communication with patients, providers, and the general public.[34]

Categories of interventions have not changed much since Parran described his approach to identifying, treating, and preventing cases in the 1930's but the specifics of how they are done will vary depending on the goal, who is targeted, and opportunities.[35–38] Opportunities for interventions will depend on where infected persons are, and resources available for finding and treating them. Social, geographic, and economic barriers are common. When outbreaks occur in areas where authorities have little experience with syphilis, consultation with others may be beneficial. Areas with insufficient resources will likely need outside help.

Interventions for adults

Screening

The US Preventive Services Task Force strongly recommends syphilis screening (grade A) for persons at increased risk for syphilis.[39] Currently, risk is increased for MSM and persons living with HIV in most areas. Other groups at risk (if any) will vary. The search for cost-effective screening interventions is challenging because many studies report test positivity among persons screened or the number screened that had newly identified infections, but do not report the number lost before they were reached for treatment or the cost per person treated (which is a more useful measure of effectiveness).[40, 41] The lab costs for syphilis screening tests are only $6,[42] so the cost of screening is mostly due to the cost of obtaining the specimen. In clinical settings, where blood is already being drawn for other purposes, such as for monitoring HIV treatment, the cost is much lower than in outreach settings where teams of people visit community venues to encourage syphilis screening. Outreach testing can be an important strategy during an outbreak,[14] but it should otherwise be considered only after exploring more efficient ways of screening such as targeting persons who are getting health care for other reasons. Jails are often good venues for screening because the incarcerated population is often at high risk for infection, and many inmates can be screened at a relatively low cost.[41, 43–47] Between 1999 and 2005, the Davidson County (Nashville, TN) jail screening program found 313 early syphilis cases (34.8% of the total

reported from the county).[45] Wherever screening is proposed, it should be based on venues frequented by previously identified cases such as neighborhoods, bathhouses, jails, or bars.[48, 49]

Interventions to increase screening in clinical settings have been most successful when they involved automatic testing as a routine part of a visit or patient reminders for screening.[40, 50] One clinic that added syphilis serology to routine blood order sets had screening increase from 3% to 90% for HIV-positive patients who had a CD4 count performed.[51] Dedicating specific staff members to assure screening has also been effective, but costly.[40] Strategies that relied on provider education alone were less effective than other approaches.[40]

In areas with high rates of syphilis among MSM, routine annual screening should be encouraged in clinics that provide care for MSM.[52] More frequent testing identifies more infections.[39, 50] Testing every three months increases the likelihood of finding infections before they progress to secondary syphilis, and thus should prevent more transmission than if the infections were found later; however, the actual impact on primary prevention is uncertain. In Australia, as annual testing of HIV-negative MSM increased from 48% to 91%, a higher percentage of infections were detected in the early latent stage.[53] The number of secondary syphilis infections also increased, but to a lesser extent. Without a randomized control group it is unclear if the observed change in secondary syphilis was lower or higher than it would have been without the increase in screening.

Treatment

Screening only has an impact if detected infections are cured, and can only prevent transmission if infected persons are cured during an early stage before they would otherwise transmit. Thus, there is a sense of urgency in treating primary and secondary syphilis, and clinicians are urged to treat suspected primary and secondary syphilis without waiting for laboratory results (which can be negative in early primary syphilis).[54] Prevention of transmission is even more likely when persons are treated after exposure to infection before they develop primary syphilis. Thus, sexual contacts (within the previous 3 months) of persons with syphilis should be treated, even if they test negative, because there is a 9–30% chance that they have an incubating infection.[55, 56]

Persons at high risk of infection, but not linked as sex partners of cases, have been treated in an effort to cure incubating infection or keep them from acquiring infection in the week following treatment. This approach was used many years ago during “syphilis blitzes” in response to big outbreaks.[57, 58] Mass treatment with azithromycin in a randomized controlled trial in Rakai, Uganda, did not lower the incidence of new syphilis (1.5 per 100 person-years in both groups).[59] Mass treatment was also used during an outbreak in Vancouver with some initial decrease in prevalence, but an eventual return to high levels led investigators to conclude that it was not successful.[60]

Pre-exposure prophylaxis (PrEP) for syphilis has been considered, in light of successful trials of antiretroviral PrEP for HIV prevention among individuals.[61] Both daily PrEP and post-exposure prophylaxis with doxycycline have decreased the risk of syphilis, gonorrhea, and chlamydia among MSM taking it in small trials over short periods of time.[62, 63]

Feasibility, and effectiveness of long-term wide-spread prophylaxis to impact transmission at the population level remain uncertain.

Partner notification

Partners of persons with syphilis are likely to be infected, so notifying them, testing them, and treating them can prevent ongoing transmission.[15] In theory, partner notification should be more effective at interrupting transmission of syphilis than it would be for other STDs because the ulcers appear 2—3 weeks after infection.[4] Therefore, partners can be located and treated before they test positive, develop lesions, and transmit to others. Because partner notification starts with an infected patient, complete investigations should always find at least one partner who has had syphilis (the source), and others if the patient has transmitted the infection. Thus, partner notification is especially useful in low-prevalence situations where screening is less productive. However, partner notification is not successful when partners are anonymous or cannot be located.[13] Major health departments in the United States have trained staff that can assist patients with notifying partners. Although randomized controlled trials have not been done for syphilis partner notification, one done for HIV found partners were more likely to be notified if the health department was involved.[64] However, the likelihood of finding infected partners has decreased over the past few decades, partly due to increases in the numbers of anonymous partners with no locating information. The number of patient interviews needed to identify one untreated partner increased from 2 in the 1950's, to 4–5 in the 1990's, and 10 in 2003.[65–67] In some areas, the number of patient interviews needed to identify a new case has been as high as 25.[68] Efforts to improve efficiency by targeting certain types of patients have not been successful because the likelihood of finding an infected partner has not been consistently associated with any characteristics of the patients (primary, secondary, or early latent stage), age, sexual orientation, or gender.[15, 68]

In light of challenges with finding partners, partner notification efforts have expanded beyond the traditional in-person notification to using telephones or other methods.[69, 70] In North Carolina, persons who could not be reached by regular partner notification efforts were referred to a single coordinator who was able to reach an additional 230 contacts via e-mail and, when that didn't work, another 14 via text messaging.[71] These approaches led to 13 new cases of syphilis and 8 persons with newly identified HIV infections which accounted for about 13% of all notifications for syphilis or HIV that year. Investigators in Monroe County, New York, used smartphone apps to search dating websites for partners when patients had no other contact information.[72] This approach successfully reached 6 of 21 partners who had been met online or via an app, and 2 more partners were notified via a website.

Behavior change interventions

Behavior change can reduce the risk of STD, but it is not so clear that counseling interventions lead to behavior change in the groups that are currently at highest risk of syphilis.[73] Condom use increased and syphilis rates decreased among MSM in the 1980's, partly due to fear of AIDS.[74] Counseling to prevent STD and HIV reduced the risk of STDs at 12 months by 20% in an RCT early in the AIDS epidemic (from 14.6% to 11.5%).[75]

However, in a major counseling trial in 2010 the incidence of new STD was similar in the counseling group (12.3%) and the information only comparison group (11.1%).[76] Community-level interventions can have a wide reach, but they are difficult to evaluate. A recent review of community interventions to increase condom use found slight increases in condom use, but no statistically significant reduction in STD.[77]

Education

Provider education is particularly important in areas where clinicians have not seen much syphilis.[78] Education should include information on: recognizing clinical manifestations, identifying persons at greatest risk based on local epidemiology, screening (especially pregnant women—early in pregnancy, again at 28–32 weeks gestation, and at delivery), treating patients with signs of syphilis while awaiting lab results, and treating recent sex partners of a case (even if test results are negative). Education alone is not as effective as clinical reminders or standing orders for increasing screening.[40] Efforts to improve provider screening practices should include establishing systems-level approaches whenever possible.[40]

Education for patients and the general public is also important, especially early in an epidemic, so that they can understand the risks, recognize rashes and painless ulcers, avoid high-risk behaviors, seek screening early in pregnancy, and support partner notification.[79] Messages can take the form of television and radio spots, posters, pamphlets, internet banner ads, websites, message boards, online chats, and community meetings depending on who is at greatest risk and where they may be found.[34] Process measures such as interviews with the target audience or website click-throughs can give an indication of reach, but it is difficult to measure the impact of a media campaign on behavior or health.[80–82]

Interventions for congenital syphilis

Penicillin is at least 97% effective in preventing congenital syphilis if infection is treated early in pregnancy.[83, 84] Because treatment is low-cost and effective, screening is cost-effective even at a very low prevalence, yet studies have found only 80%–85% of women had been screened during pregnancy.[85, 86] One study found 96.3% of pregnant women with Medicaid who had prenatal care were screened, though it was not clear how many were screened early in pregnancy.[87] Many congenital syphilis cases are attributable to lack of prenatal care.[26] To reduce the risk of syphilitic stillbirths, women should be screened at their first prenatal visit.[28] Women may also acquire infection during pregnancy so it is important to rescreen women who live in high-prevalence areas. Treatment is less effective if given within 30 days of delivery,[84] so re-screening should be done late enough to catch most women who acquire infection but early enough to allow treatment 30 days before delivery (28–32 weeks).

The effectiveness of screening was demonstrated in a recent study from Florida and Louisiana.[88] Of 710 infected pregnant women, 470 potential cases of congenital syphilis were prevented by screening in the first 2 trimesters, and an additional 85 were prevented by screening at 28–32 weeks. Of the 155 cases (22% of 710) that were not prevented: 28% had insufficient or late treatment (often due to late screening or prematurity), 25% had not been

tested early enough (most had not sought prenatal care), 23% had tested negative early in pregnancy and were not rescreened, 9% tested (or re-tested) negative at 22–32 weeks and still had babies with congenital syphilis, 10% were apparently re-infected after treatment, and 6% had evidence of congenital syphilis despite appropriate treatment. Other reports have found similar explanations for babies with congenital syphilis, with some variation in the relative frequencies.[89–91]

There is no question that screening pregnant women for syphilis can prevent congenital syphilis,[92] the issue is how to assure that women are screened and treated. Two randomized trials, both done outside of the United States, have evaluated screening during pregnancy to prevent congenital syphilis.[93] One study, in South Africa, found no reduction in perinatal mortality when onsite rapid testing was compared to routine testing, however, the comparison clinics screened 98% of women and treatment rates were similar in both groups (64% vs 69%).[94] The other study was a cluster randomized trial in Mongolia that had a comparison screening rate of 80%. Increasing screening to over 99%, and increasing treatment with one-stop services that included rapid syphilis testing and treatment at the first visit and third trimester, reduced the number of congenital syphilis cases by 94% (from 15 to 1).[95] A review of 8 non-randomized interventions (including a 5-pronged intervention in Milwaukee)[96] concluded that interventions had reduced syphilis-attributable stillbirth and perinatal death by 50%.[97]

Prevention of all congenital syphilis requires prevention of syphilis among women because it is not possible to catch all infections in pregnant women in time to prevent the serious complications of congenital syphilis.[24, 25, 88] This previously aspirational goal is now feasible in many contexts. Unlike outbreaks in MSM, many recent outbreaks among heterosexuals have been stopped by intensive efforts using combinations of interventions.[20, 98, 99]

Measuring impact

Interventions are synergistic so usually multiple interventions are implemented at the same time. Furthermore, risks in communities are constantly changing. Therefore, it is not easy to tell if an intervention is reducing the incidence of infection, but process measures are very useful indicators. Interventions that treat many early infections are more effective than those that reach only a few late infections. There is a tendency to think that interventions are not working if disease rates are increasing, or they are working if rates are going down. However, without a comparison group it is hard to tell if an intervention has influenced rates, or if rates have changed for other reasons.

Conclusions

The syphilis elimination effort of 1999 was launched with the understanding that high rates of syphilis identified communities where there was a fundamental failure of basic public health capacity to control infectious diseases.[100] Since then, the context has changed and the goal of syphilis elimination has been elusive. The context in many areas of the United States is very high rates among MSM who are not very concerned about syphilis because it is easy

to treat, and illness among adults is now most often minor.[101,102] Despite many attempts, no area has been able to stop the continuing increase in infections among MSM. Further research is needed to identify combinations of interventions that can reduce the incidence of syphilis among MSM. Meanwhile, routine screening and treatment of MSM can keep disease rates low by preventing progression from infection to disease (secondary prevention)

Congenital syphilis was at a near all-time low rate in 2012 but there have since been major increases, first in a few areas, and then in others, with devastating consequences. Comprehensive prenatal screening can prevent about 75% of congenital syphilis. Aggressive efforts have prevented all congenital syphilis in some areas by stopping heterosexual outbreaks and eliminating infections among women (primary prevention). Thus, the biggest contextual challenge for many programs is how to focus on secondary prevention in one population and primary prevention in the other.

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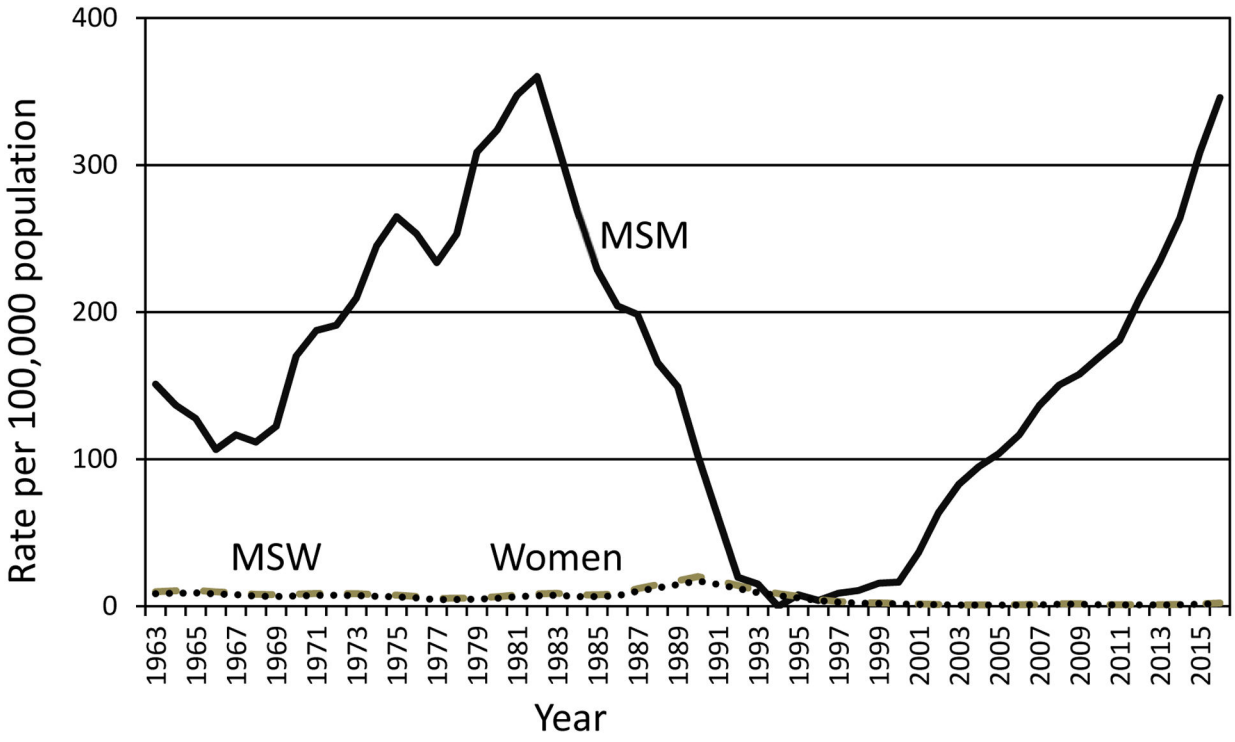


Figure 1.

Primary and secondary syphilis: estimated annual rate per 100,000 population by sex and sex of sex partner, United States, 1963–2016.

MSM: men who had sex with men. MSW: men who had sex with women only. Estimated using modified Heffelfinger M:F rate ratio of 1.1236, assuming no MSM had syphilis in 1994, and estimating 3.9% of men are MSM[19]

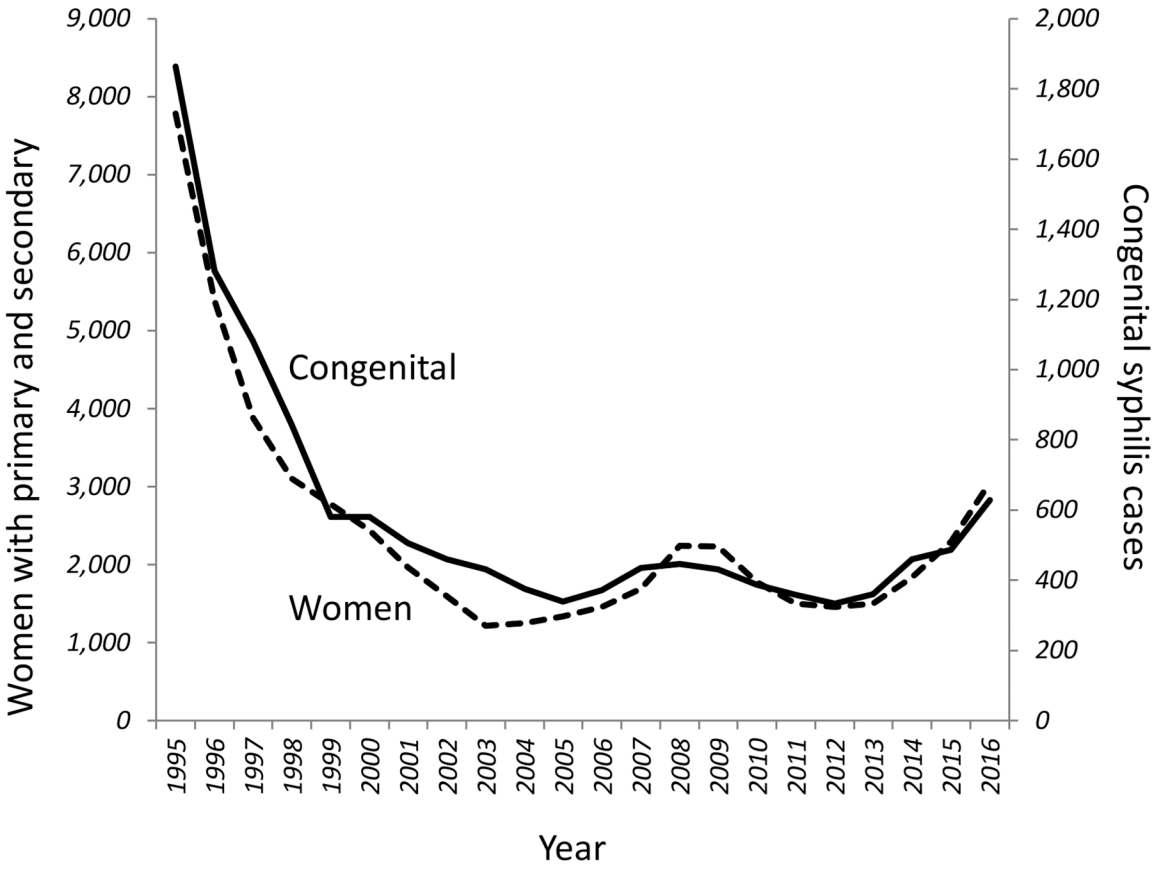
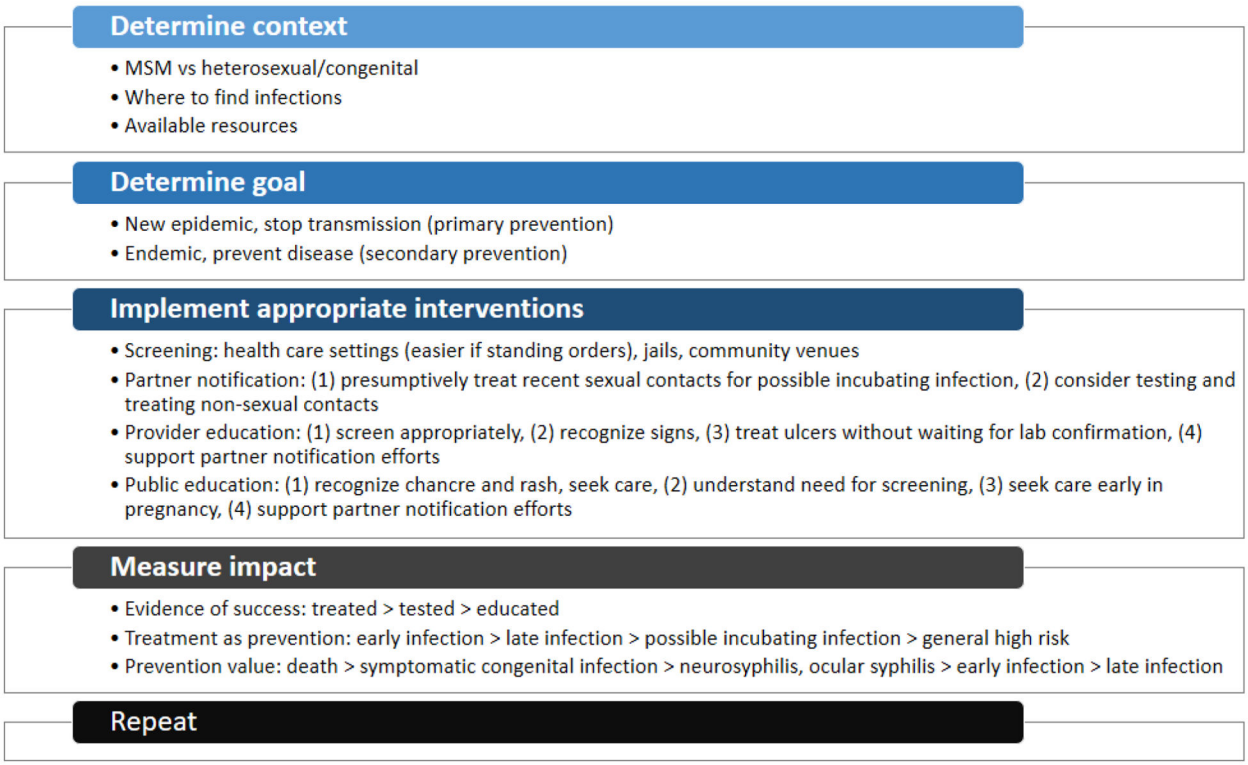


Figure 2.
Reported primary and secondary syphilis among women and congenital syphilis by year of birth, United States, 1995–2016.



Text box 1.
Steps for implementing a context appropriate intervention for syphilis.