Expanding syphilis testing: A scoping review of syphilis testing interventions among key populations

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ABSTRACT

Introduction

Syphilis is an important sexually transmitted infection (STI). Despite inexpensive and effective treatment, few key populations receive syphilis testing. Innovative strategies are needed to increase syphilis testing among key populations.

Areas covered

This scoping review focused on strategies to increase syphilis testing in key populations (men who have sex with men (MSM), sex workers, people who use drugs, transgender people, and incarcerated individuals).

Expert commentary

We identified many promising syphilis testing strategies, particularly among MSM. These strategies are separated into diagnostic, clinic-based, and non-clinic based. In terms of diagnostics, self-testing, dried blood spots, and point-of-care testing can decentralize syphilis testing. Effective syphilis self-testing pilots suggest the need for further attention and research. In terms of clinic-based strategies, modifying default clinical procedures can nudge physicians to more frequently recommend syphilis testing. In terms of non-clinic based strategies, venue-based screening (e.g. in correctional facilities, drug rehabilitation centres) and mobile testing units have been successfully implemented in a variety of settings. Integration of syphilis with HIV testing may facilitate implementation in settings

where individuals have increased sexual risk. There is a strong need for further syphilis testing research and programs.

1. INTRODUCTION

Syphilis is a perennial global public health problem[1]. Syphilis is one of the four most common curable sexually transmitted infections (STI), with an estimated 5.6 million individuals age 15-49 years newly infected in 2012[2]. Concern over syphilis related morbidity and mortality of women and their babies has resulted in international attention focused on the elimination of mother-to-child transmission of syphilis[3]. However, there is relatively less literature devoted to screening key populations at high risk for syphilis: sex workers (SW), men who have sex with men (MSM) and transgender people, people who use drugs (PWUD), and those in incarceration. Although the term key population was developed with reference to HIV, in this paper we refer to the same groups related to syphilis. Without effective interventions, syphilis epidemics in key populations are likely to expand[1].

In the absence of a vaccine, controlling syphilis relies on timely diagnosis and treatment of those who are infected. In particular, modelling studies suggest frequent key population syphilis testing can reduce prevalence[4,5]. WHO guidelines recommend syphilis testing for sexually active members of key populations at least once a year, and testing every 3 months for those at higher risk[3]. Yet most countries do not have specific syphilis testing guidelines or dedicated resources for syphilis prevention and control. Syphilis control measures have been plagued by challenges related to diagnostics, clinic and non-clinic related barriers. From a diagnostics perspective, limited accessibility to diagnostics in some settings, unfavourable incentive or reimbursement structures, and related health systems issues

contribute to difficulties encouraging syphilis testing in key populations[2]. Clinic-related barriers to syphilis testing include lack of national guidelines, confusing serologies, lack of time/staff, discomfort with sexual history taking and genital examination, lack of testing and treatment knowledge among providers[6]. Non-clinic related barriers include stigma associated with STI and testing, patient perceptions of low STI risk, burdensome testing procedures and concern over confidentiality of status[7,8]. Accurate knowledge of one's STI status is critical as early diagnosis and treatment results in reduced morbidity and risk of onward transmission.

The review literature to date on syphilis testing has focused on advances in diagnostics but not public health strategies to improve syphilis testing in key populations[9,10]. The aim of this scoping review is to summarize original research on syphilis testing strategies among key populations, focused on diagnostics[9,11], clinic-based testing strategies, and non-clinic-based testing strategies[12-16]. We highlight key examples that illustrate effective strategies and suggest areas for future research.

2. METHODS

We used a scoping review methodology to examine the literature on syphilis testing strategies in key populations[17]. We searched PubMed and Google Scholar for studies published in English from January 1st 2000 to November 1st 2017. Search terms used were [syphilis AND (screening OR test OR surveillance OR diagnosis OR intervention OR trial OR demonstration OR project OR program). We also searched for results according to the key populations, for example adding (men OR men who have sex with men OR gay OR trans* OR transgender OR prisoner OR people who use drugs OR people who inject drugs OR drug user

OR injection drug user OR incarcerated OR sex worker). Hand searches of the references of relevant manuscripts was also performed.

We present the summarized information under the following categories (Figure 1): 1) novel diagnostics for syphilis testing, 2) clinic-based strategies, and 3) non-clinic and community based strategies. Finally, we provide an expert commentary to identify gaps in the existing evidence and suggestions for future research activity.

3. RESULTS

3.1 Innovations in syphilis diagnostics

Syphilis diagnostics have not changed substantially in the past century. Darkfield microscopy has been used to detect the spirochete of syphilis since its discovery in 1905 by Schaudinn and Hoffman[18]. Subsequently, the first serological test was developed in 1910 and the first test specific for treponemal antibody in 1949[18]. Traditionally, screening algorithms begin with a non-treponemal specific antibody test (e.g. rapid plasma reagin, RPR) followed by a treponemal specific antibody test (e.g. *Treponema pallidum* particle agglutination, TPPA). Alternatively, specimen batch testing using a reverse diagnostic algorithm by using a treponemal specific antibody test first followed by a non-treponemal specific antibody test has made testing more cost-efficient and reduced the rate of false-positive RPRs[19,20]. Other new diagnostics such as automated chemilluminescent micro-particle immunoassay (CLIA) have been developed[21]. However, all these tests are still time consuming and requires laboratory staff with technical expertise and specialized equipment.

Though traditional testing for syphilis is clinic-based, recent developments have enabled decentralized key population testing. This includes dried blood spots, point-of-care testing, and self-testing.

3.1.1 Dried blood spots (DBS)

DBS is a form of sampling where blood is blotted and dried on filter paper, and sent to a laboratory for serological testing. This is a form of self-collection, but not self-testing. Several studies among MSM suggest willingness to self-collect testing specimens at home[13,14]. DBS syphilis testing has not yet been approved by regulatory agencies. DBS advantages include the following: specimens can be returned through the postal service for processing; allows integration with testing for other infections such as HIV, hepatitis B and C[14,22,23]. A study of 217 MSM living in the Netherlands evaluated the feasibility and acceptability of DBS syphilis testing[14]. The majority (80%) of men found DBS acceptable. Importantly, there was no difference in the adequacy of the specimen collected to enable serological testing between self-collected DBS compared to health worker collected DBS, and overall 91% of DBS had sufficient specimen to test for three infections: HIV, hepatitis B and syphilis. Using routine diagnostics as the gold standard, the sensitivity of DBS for syphilis was 91% and specificity was 99%[14].

3.1.2 Point-of-care (POC) testing

POC testing involves conducting syphilis testing with results given within a short time, at or near the site of patient care by trained health providers[24]. POC testing by trained outreach staff or community health workers might be an important strategy to reach key population in addition to health providers. POC tests to detect treponemal antibodies are increasingly

accessible and perform well in the field[9,11]. These automated POC platforms are portable, enable anonymous testing and are relatively easy to use, eliminating the need for venepuncture and laboratory support. Important trade-offs are that though POC tests have generally comparable performance characteristics to laboratory based testing, POC tests have poorer sensitivity, especially at lower RPR levels (<1:16)[25]. Another limitation is that most POC syphilis tests detect only anti-treponemal specific antibodies. However, there is one commercially available POC test in some countries which incorporates testing for both treponemal and non-treponemal antibodies. Compared to conventional laboratory testing, it has a sensitivity of 89.8% (95% CI: 87.3-91.9) and specificity of 99.3% (95% CI: 97.0-99.9) for treponemal antibodies, and sensitivity of 94.2% (95% CI: 91.8-96.0) and specificity of 62.2% (95% CI: 57.5-66.6) for non-treponemal antibodies[26]. Development of further combination point-of-care tests would be useful for those treated for past syphilis or in settings with endemic yaws.

There has also been increasing interest in concurrent POC testing of syphilis and HIV using the same specimen (i.e. dual testing), given their similar transmission routes. The feasibility of introducing dual POC testing has been tested in a wide variety of settings: STI clinic attendees in the US[27], pregnant women in rural Uganda[28] and Nepal[29], MSM and transgender women in Peru[30], and female sex workers (FSW) in Johannesburg[31]. Dual POC testing is accurate[32,33] and cost-effective among pregnant women compared to single rapid diagnostic test[34]. Currently, there is WHO guidance of the use of dual POC testing in antenatal women, but not for key populations[35].

3.1.3 Syphilis self-testing

Syphilis self-testing is the process whereby an individual collects a specimen, performs the test and interprets the result. This can be done unsupervised at home, supervised in community clinics, or in other settings. This method of testing has the advantages of providing a user-friendly, rapid, accurate and private means of testing – many of these characteristics are important to key populations[36]. An expanding literature on HIV self-testing[37,38] alongside policy momentum led the World Health Organization to develop guidelines recommending HIV self-testing[39]. Accordingly, the concept of syphilis self-testing has been implemented among MSM in the Netherlands[40] and China[36]. This approach could help to increase first-time testing among individuals who do not want to seek care in a clinic-based setting. Although syphilis self-test kits are available for purchase[41,42], more evidence of this approach is needed to develop other pilot programs.

3.2 Clinic-based testing strategies

Clinic-based testing strategies seek to improve screening uptake by modifying existing clinical practice, with the aim to motivate greater testing uptake, and increase detection of asymptomatic syphilis. These interventions typically target structural, provider, or patient levels.

3.2.1 Structural interventions

The two main types of structural interventions involve those that lower barriers to sexual healthcare access and those that modify clinic flow practices to improve service delivery. Interventions to address barriers to care have largely focused on key populations, often through the creation of specialized clinics for FSW[43] or MSM[44], provision of clinic vouchers[45], or implementation of a culturally sensitive and comprehensive care models[46]. Strategies to

address clinic procedures include those routinizing syphilis testing[47]—particularly for people living with HIV[48-50]—through use of novel diagnostic tools for same day diagnosis[51], and the use of technology (e.g. internet, text messages) to enhance public health services such as test result notification[52,53] or partner notification[54,55].

3.2.2 Provider-level interventions

Provider-level interventions to improve syphilis screening have consisted of task shifting, integration with HIV services, and physician reminders. Task shifting is where responsibility for certain clinical tasks are transferred, when appropriate, to less specialized health care staff. Several sexual health clinics in the United States, Australia and the Netherlands, have adopted nurse-led approaches in which nurses stand in for physicians as the first-line sexual health providers[56]. In the United States[57] and Ireland[58], primary care physicians have received specialised training in sexual health service provision, whereas a pilot study in the United Kingdom embedded sexual health specialists in HIV care clinics[59]. These strategies decentralize sexual health services and improve detection of more asymptomatic cases by introducing screening into primary care settings. Integration of syphilis and HIV testing at clinics is another strategy. One study[60] and one large implementation project[61] suggest that integration of syphilis and HIV testing is feasible and acceptable in clinical settings. Finally, automated reminders have been used to encourage syphilis counselling and testing among MSM in clinics[4,62].

3.2.3 Patient-level interventions

Syphilis screening strategies at the patient level have included internet and text-message assisted strategies to regularly remind patients to initially screen[63] or retest for syphilis[64].

Encouraging results from these two studies support the use of text messages for promoting syphilis testing. Monetary incentives have been used to improve testing for HIV and other STIs[65,66], including syphilis testing[66]. The syphilis test incentive study offered individuals with drug addiction or unstable housing small rewards for obtaining their syphilis results or seeking treatment if required[66]. Further research is needed to assess the cost-effectiveness for providing financial incentives to increase syphilis testing uptake.

3.3 Non-clinic and community based testing strategies

Although screening for syphilis to date has primarily been conducted in clinic-based settings [10,67], advances in STI diagnostics have increased the number of non-clinic and community-based settings where syphilis testing is feasible[12-14,68]**.** Advantages of non-clinic and community-based testing include reaching individuals who may not seek clinical services, and integrating testing within existing community-based services in collaboration with local partners. Community-based syphilis testing strategies for key populations through outreach at entertainment or commercial sex venues and mobile testing units have proven to be effective in reaching key populations[31,69]. These testing approaches have been integrated into routine STI surveillance systems[70]. Furthermore, internet and social network based testing and promotion have been used to scale up earlier diagnosis of syphilis in key populations[71-73].

This section reviews syphilis testing interventions outside of clinic settings, including screening conducted in venues (such as correctional settings and drug rehabilitation facilities), mobile sites (such as perioidic outreach services provided at entertainment/sex venues and through mobile testing units), and through campaigns using social networks.

3.3.1 Venue-based syphilis testing

Universal screening for syphilis has been provided in jails and other correctional settings in several countries[50,69,74-76]. Success of the venue-based strategy depends on the local epidemiology of syphilis. Data from STI screening conducted at correctional facilities in the United States suggests a high syphilis prevalence in the incarcerated populations, and programs have been particularly successful for identifying syphilis outbreaks in heterosexuals[76-80]. Although syphilis testing in correctional facilities introduces a range of special challenges, it also provides unique opportunities for expanding syphilis testing[50,75].

Similarly, routine screening of syphilis in PWUD have been conducted at drug use rehabilitation and treatment facilities, including methadone maintenance treatment (MMT) clinics and syringe exchange programs in a few countries[81-90]. For example, syphilis screening is integrated into the national drug rehabilitation system as a standard medical service for PWUD in China[87,91]. PWUD receiving MMT are routinely screened for syphilis together with HIV and HCV[87]. Findings demonstrated the feasibility and cost-effectiveness of integrating syphilis screening into existing PWUD programs[87,88].

3.3.2 Mobile testing sites

Mobile STI screening programs are particularly well suited for populations in rural, low-income communities or areas with disproportionately high syphilis burden[92-95]. Mobile van testing services have successfully provided services at community events (e.g. Gay Pride parades and parties) or at sex/entertainment venues where higher risk sex often takes place[96]. Mobile vans have also been used to deliver syphilis testing services to target high

risk populations in other developing and developed countries, such as Russia[93,97-100], Peru[101] and Guatemala[102]. This research suggests that mobile testing units effectively expand first-time syphilis testing among a subset of key populations that do not access clinical services [95,96,102].

Periodic outreach syphilis testing services have been conducted at entertainment or sex venues, for example, brothels, gay bars, bathhouses. These programs have increased syphilis testing among PWUD[81,98,103-105], [106-108], MSM[31,51,109-111] and transgender people[112]. For example, health outreach teams in two Chinese cities offered free onsite rapid syphilis testing to approached at various types of commercial sex venues[107]. Among the FSW who were offered rapid syphilis testing, 95% accepted the test; 7% tested positive, among which 75% agreed to visit an STI clinic for confirmatory testing, and 66% were willing to notify their partners of the test result[107].

3.3.3 Use of new communication technologies to increase syphilis testing

We define new communication technologies as mass communication using digital technologies such as social networking platforms. Public campaigns through targeted messaging interventions have been used to increase syphilis knowledge and testing. These programs have focused on MSM and transgender people[110,113,114]. Mixed findings were reported. For example, a syphilis awareness public campaign targeting MSM in eight U.S. cities using social marketing approach reported an increased awareness of syphilis in some cities and increased syphilis testing associated with campaign participation[113]. However, the "Check Yourself "public campaign conducted in Los Angeles in the U.S. did not find a significant association between campaign awareness and syphilis testing in MSM[114]. Among

technology-focused testing strategies, crowdsourcing is another approach to developing new syphilis testing campaigns. Crowdsourcing is the process of having a group solve a problem and then sharing the solution with the public.[115] Crowdsourcing has been used to solicit novel content for promotional images, videos, and HIV testing strategies. A stepped wedge trial randomized controlled trial evaluating this approach is underway and includes syphilis testing as a secondary outcome[116]. Cross-sectional data from this study suggested that dual HIV/syphilis self-testing promoted through the internet could be a feasible approach for increasing syphilis testing among MSM[117].

There is a small but growing literature that examines the internet as a platform for distributing syphilis test kits, self-collection kits, or non-clinical testing[15,118-121]. Two pilot studies allow MSM to download a referral letter for presentation at a testing laboratory for a syphilis test; then results were received online[122,123]. However, both sites found that fewer than 10% of those who requested a letter received a test kit[122,123]. Other studies have examined new technologies as tools to promote syphilis testing[15,16,124-126] including using Facebook and Twitter[124,125]; online research surveys on gay websites[15,16]. However, linkage to clinic-based syphilis testing from banner advertisements was less than 20% in both studies that measured it[15,16]. A study which evaluated the effect of a social network-based campaign on STI testing use in youths reported a significant increase in syphilis testing (from 5% to 19%, pre- and post-campaign)[124]. Another study evaluating automated text message and email reminders promoting syphilis re-testing among MSM increased detection of syphilis[63].

4. EXPERT COMMENTARY

Several key insights can be gained from this review. Table 1 provides a summary of syphilis testing strategies organized by key population. This suggests that most syphilis testing programs have focused on MSM, with comparatively less attention devoted to SW, incarcerated individuals, PWUD and transgender populations. These gaps underscore the future work needed to assess these identified strategies in other key populations, as they may share similar structural and societal disadvantages related to accessing healthcare, key populations also have critical differences from one another. Costs of these programs are quite variable and not well-studied. Future cost-effectiveness studies reporting the cost per test performed and cost per syphilis case successfully treated in key populations may be useful metrics. The local epidemiology of syphilis ought to drive which strategy to use and how resources available should be allocated to key populations within each setting. Programs using mobile testing units are in general more costly per case identified (and treated) than other strategies.[126] However, integration of syphilis testing into an existing program such as one that is testing for HIV is generally less costly.[60] Structural-level interventions may be more cost-effective than provider- or patient-level interventions, although further empirical research is needed.[127] In addition, given the extensive literature on HIV testing interventions among key populations,[128,129] this evidence may help inform the design of syphilis testing strategies. While there are notable differences in these two diseases, the shared opportunities are also substantial. Integrated HIV/syphilis testing programs,[60] key population friendly services, and related projects require further implementation research.

Table 1 Examples of strategies aimed at increasing syphilis testing in key populations

	MSM	SW	Incarcerated	PWUD	Transgender

Diagnostics					
Dried blood spot	14	23			
Point-of-care testing	30	31		130	131
Self-testing	36,40				
Clinic based					
Structural	47-49	43,45	51		
Provider	4,59,62				
Patient	63,64				
Non-clinic based strategies					
Venue-based	31,78,97,109-111	91,132		81,83-86,98,103-105	
Mobile testing	96,97,101,102,110	92,102,108		93,97-100	101,102
New communications technology	15,63,110,113,114,124-126,133				134,135

MSM = men who have sex with men; PWUD = people who use drugs; SW = sex workers

While recent advancements in syphilis diagnostics have decentralized testing, further research is needed on syphilis test self-collection and self-testing. Given the widespread adoption of HIV self-testing and growing infrastructure to support HIV self-testing, further research on syphilis self-testing is warranted. Another major gap in the literature pertaining to diagnostics, is the lack of discussion regarding innovations in syphilis testing methodologies, e.g. how to rapidly identify active syphilis and bypass the current limitation of POC test kits being unable to accurately distinguish past treated infection from active infection.

Clinic-based strategies are relatively simple tweaks to existing protocols to improve syphilis testing uptake in key populations. By modifying clinical practices, these interventions

leverage an existing infrastructure and patient population to increase screening in key populations. Other clinic-based interventions that have been implemented for control of other curable STIs provide guidance for future syphilis control approaches, or integrated control of multiple STIs. Some such strategies include behavioural counselling delivered in clinical settings[136,137], automated reminders for providers built into electronic health record systems[138,139], and provider-level monetary incentives[140,141]. Clinic-based strategies should be coupled with simultaneous efforts to improve health seeking behaviours in key populations and reduce individual and structural barriers to access care.

While existing studies showed that non-clinic based programs were effective in improving the access of key populations to syphilis screening services, particularly among those who were more hidden and had higher STI risks[12,69,142], few studies have evaluated linkage to care and related services. The gap between testing and treatment services could compromise the effectiveness of these strategies[143]. In addition, advances in new syphilis testing approaches have yet to translate into clinic seeking and clinic service uptake. Lessons can be learnt from the larger HIV new communications technology literature when designing new syphilis testing strategies[144].

5. FIVE-YEAR VIEW

As syphilis remains a persistent global public health threat, innovative ways to generate demand for syphilis testing are needed. Challenge contests and related crowdsourcing approaches could help to identify and nurture local innovation.[115] Local surveillance data on syphilis diagnosis to delineate the scope of the problem and better data on cost-effectiveness may inform policy makers. With further advancements in diagnostic

technologies, there may be a greater role for syphilis self-testing in reaching key populations. In addition, as syphilis testing becomes increasingly decentralized, there is an urgent need to ensure quality of test kits and linkage to comprehensive services.

6. KEY ISSUES

- Syphilis is an important sexually transmitted infection and despite inexpensive and effective treatment, few key populations receive syphilis testing. In particular, key populations in need of greater uptake of syphilis testing includes men who have sex with men (MSM), sex workers, people who use drugs, transgender people, and incarcerated individuals.
- Recent strategies to improve syphilis testing in these key populations can be separated into diagnostic, clinic-based, and non-clinic based strategies.
- In terms of diagnostics, self-testing, dried blood spots, and point-of-care testing can decentralize syphilis testing.
- In terms of clinic-based strategies, slight modifications of default clinical procedures can nudge physicians to more frequently recommend key population syphilis testing.
- In terms of non-clinic-based strategies, venue-based screening and mobile testing units have been successfully implemented. Together with harnessing social network technologies, syphilis self-testing provides an important tool to address the unmet needs of marginalized populations, particularly when it is integrated with other existing services (e.g. HIV testing).

7. CONCLUSION

The strategies identified from our review have played an important role in improving syphilis testing targeted towards hidden and hard-to-reach members of key populations who uncommonly access clinic-based services. If the syphilis epidemics among key populations are to be controlled, further work is needed to assess the cost-effectiveness and scalability of these strategies.

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