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

3

4 **Jason Ong, Hongyun Fu, M. Kumi Smith, Joseph D. Tucker**

5

6

7 **ABSTRACT**

8 **Introduction**

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

12 **Areas covered**

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

16 **Expert commentary**

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

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

28

29 **1. INTRODUCTION**

30 Syphilis is a perennial global public health problem¹. Syphilis is one of the four most
31 common curable sexually transmitted infections (STI), with an estimated 5.6 million
32 individuals age 15-49 years newly infected in 2012². Concern over syphilis related morbidity
33 and mortality of women and their babies has resulted in international attention focused on
34 the elimination of mother-to-child transmission of syphilis³. However, there is relatively less
35 literature devoted to screening key populations at high risk for syphilis: sex workers (SW),
36 men who have sex with men (MSM) and transgender people, people who use drugs
37 (PWUD), and those in incarceration. Although the term key population was developed with
38 reference to HIV, in this paper we refer to the same groups related to syphilis. Without
39 effective interventions, syphilis epidemics in key populations are likely to expand¹.

40

41 In the absence of a vaccine, controlling syphilis relies on timely diagnosis and treatment of
42 those who are infected. In particular, modelling studies suggest frequent key population
43 syphilis testing can reduce prevalence^{4,5}. WHO guidelines recommend syphilis testing for
44 sexually active members of key populations at least once a year, and testing every 3 months
45 for those at higher risk³. Yet most countries do not have specific syphilis testing guidelines
46 or dedicated resources for syphilis prevention and control. Syphilis control measures have
47 been plagued by challenges related to diagnostics, clinic and non-clinic related barriers.
48 From a diagnostics perspective, limited accessibility to diagnostics in some settings,
49 unfavourable incentive or reimbursement structures, and related health systems issues

50 contribute to difficulties encouraging syphilis testing in key populations². Clinic-related
51 barriers to syphilis testing include lack of national guidelines, confusing serologies, lack of
52 time/staff, discomfort with sexual history taking and genital examination, lack of testing and
53 treatment knowledge among providers⁶. Non-clinic related barriers include stigma
54 associated with STI and testing, patient perceptions of low STI risk, burdensome testing
55 procedures and concern over confidentiality of status^{7,8}. Accurate knowledge of one's STI
56 status is critical as early diagnosis and treatment results in reduced morbidity and risk of
57 onward transmission.

58

59 The review literature to date on syphilis testing has focused on advances in diagnostics but
60 not public health strategies to improve syphilis testing in key populations^{9,10}. The aim of this
61 scoping review is to summarize original research on syphilis testing strategies among key
62 populations, focused on diagnostics^{9,11}, clinic-based testing strategies, and non-clinic-based
63 testing strategies¹²⁻¹⁶. We highlight key examples that illustrate effective strategies and
64 suggest areas for future research.

65

66 **2. METHODS**

67 We used a scoping review methodology to examine the literature on syphilis testing
68 strategies in key populations¹⁷. We searched PubMed and Google Scholar for studies
69 published in English from January 1st 2000 to November 1st 2017. Search terms used were
70 [syphilis AND (screening OR test OR surveillance OR diagnosis OR intervention OR trial OR
71 demonstration OR project OR program)]. We also searched for results according to the key
72 populations, for example adding (men OR men who have sex with men OR gay OR trans* OR
73 transgender OR prisoner OR people who use drugs OR people who inject drugs OR drug user

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

76

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

81

82 **3. RESULTS**

83

84 **3.1 Innovations in syphilis diagnostics**

85 Syphilis diagnostics have not changed substantially in the past century. Darkfield microscopy
86 has been used to detect the spirochete of syphilis since its discovery in 1905 by Schaudinn
87 and Hoffman¹⁸. Subsequently, the first serological test was developed in 1910 and the first
88 test specific for treponemal antibody in 1949¹⁸. Traditionally, screening algorithms begin
89 with a non-treponemal specific antibody test (e.g. rapid plasma reagin, RPR) followed by a
90 treponemal specific antibody test (e.g. *Treponema pallidum* particle agglutination, TPPA).
91 Alternatively, specimen batch testing using a reverse diagnostic algorithm by using a
92 treponemal specific antibody test first followed by a non-treponemal specific antibody test
93 has made testing more cost-efficient and reduced the rate of false-positive RPRs^{19,20}. Other
94 new diagnostics such as automated chemiluminescent micro-particle immunoassay (CLIA)
95 have been developed²¹. However, all these tests are still time consuming and requires
96 laboratory staff with technical expertise and specialized equipment.

97

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

101

102 **3.1.1 Dried blood spots (DBS)**

103 DBS is a form of sampling where blood is blotted and dried on filter paper, and sent to a
104 laboratory for serological testing. This is a form of self-collection, but not self-testing.

105 Several studies among MSM suggest willingness to self-collect testing specimens at

106 home^{13,14}. DBS syphilis testing has not yet been approved by regulatory agencies. DBS

107 advantages include the following: specimens can be returned through the postal service for

108 processing; allows integration with testing for other infections such as HIV, hepatitis B and

109 C^{14,22,23}. A study of 217 MSM living in the Netherlands evaluated the feasibility and

110 acceptability of DBS syphilis testing¹⁴. The majority (80%) of men found DBS acceptable.

111 Importantly, there was no difference in the adequacy of the specimen collected to enable

112 serological testing between self-collected DBS compared to health worker collected DBS,

113 and overall 91% of DBS had sufficient specimen to test for three infections: HIV, hepatitis B

114 and syphilis. Using routine diagnostics as the gold standard, the sensitivity of DBS for syphilis

115 was 91% and specificity was 99%¹⁴.

116

117 **3.1.2 Point-of-care (POC) testing**

118 POC testing involves conducting syphilis testing with results given within a short time, at or

119 near the site of patient care by trained health providers²⁴. POC testing by trained outreach

120 staff or community health workers might be an important strategy to reach key population

121 in addition to health providers. POC tests to detect treponemal antibodies are increasingly

122 accessible and perform well in the field^{9,11}. These automated POC platforms are portable,
123 enable anonymous testing and are relatively easy to use, eliminating the need for
124 venepuncture and laboratory support. Important trade-offs are that though POC tests have
125 generally comparable performance characteristics to laboratory based testing, POC tests
126 have poorer sensitivity, especially at lower RPR levels (<1:16)²⁵. Another limitation is that
127 most POC syphilis tests detect only anti-treponemal specific antibodies. However, there is
128 one commercially available POC test in some countries which incorporates testing for both
129 treponemal and non-treponemal antibodies. Compared to conventional laboratory testing,
130 it has a sensitivity of 89.8% (95% CI: 87.3-91.9) and specificity of 99.3% (95% CI: 97.0-99.9)
131 for treponemal antibodies, and sensitivity of 94.2% (95% CI: 91.8-96.0) and specificity of
132 62.2% (95% CI: 57.5-66.6) for non-treponemal antibodies²⁶. Development of further
133 combination point-of-care tests would be useful for those treated for past syphilis or in
134 settings with endemic yaws.

135

136 There has also been increasing interest in concurrent POC testing of syphilis and HIV using
137 the same specimen (i.e. dual testing), given their similar transmission routes. The feasibility
138 of introducing dual POC testing has been tested in a wide variety of settings: STI clinic
139 attendees in the US²⁷, pregnant women in rural Uganda²⁸ and Nepal²⁹, MSM and
140 transgender women in Peru³⁰, and female sex workers (FSW) in Johannesburg³¹. Dual POC
141 testing is accurate^{32,33} and cost-effective among pregnant women compared to single rapid
142 diagnostic test³⁴. Currently, there is WHO guidance of the use of dual POC testing in
143 antenatal women, but not for key populations³⁵.

144

145 **3.1.3 Syphilis self-testing**

146 Syphilis self-testing is the process whereby an individual collects a specimen, performs the
147 test and interprets the result. This can be done unsupervised at home, supervised in
148 community clinics, or in other settings. This method of testing has the advantages of
149 providing a user-friendly, rapid, accurate and private means of testing – many of these
150 characteristics are important to key populations³⁶. An expanding literature on HIV self-
151 testing^{37,38} alongside policy momentum led the World Health Organization to develop
152 guidelines recommending HIV self-testing³⁹. Accordingly, the concept of syphilis self-testing
153 has been implemented among MSM in the Netherlands⁴⁰ and China³⁶. This approach could
154 help to increase first-time testing among individuals who do not want to seek care in a
155 clinic-based setting. Although syphilis self-test kits are available for purchase^{41,42}, more
156 evidence of this approach is needed to develop other pilot programs.

157

158 **3.2 Clinic-based testing strategies**

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

163

164 **3.2.1 Structural interventions**

165 The two main types of structural interventions involve those that lower barriers to sexual
166 healthcare access and those that modify clinic flow practices to improve service delivery.
167 Interventions to address barriers to care have largely focused on key populations, often
168 through the creation of specialized clinics for FSW⁴³ or MSM⁴⁴, provision of clinic vouchers⁴⁵,
169 or implementation of a culturally sensitive and comprehensive care models⁴⁶. Strategies to

170 address clinic procedures include those routinizing syphilis testing⁴⁷—particularly for people
171 living with HIV⁴⁸⁻⁵⁰—through use of novel diagnostic tools for same day diagnosis⁵¹, and the
172 use of technology (e.g. internet, text messages) to enhance public health services such as
173 test result notification^{52,53} or partner notification^{54,55}.

174

175 **3.2.2 Provider-level interventions**

176 Provider-level interventions to improve syphilis screening have consisted of task shifting,
177 integration with HIV services, and physician reminders. Task shifting is where responsibility
178 for certain clinical tasks are transferred, when appropriate, to less specialized health care
179 staff. Several sexual health clinics in the United States, Australia and the Netherlands, have
180 adopted nurse-led approaches in which nurses stand in for physicians as the first-line sexual
181 health providers⁵⁶. In the United States⁵⁷ and Ireland⁵⁸, primary care physicians have
182 received specialised training in sexual health service provision, whereas a pilot study in the
183 United Kingdom embedded sexual health specialists in HIV care clinics⁵⁹. These strategies
184 decentralize sexual health services and improve detection of more asymptomatic cases by
185 introducing screening into primary care settings. Integration of syphilis and HIV testing at
186 clinics is another strategy. One study⁶⁰ and one large implementation project⁶¹ suggest that
187 integration of syphilis and HIV testing is feasible and acceptable in clinical settings. Finally,
188 automated reminders have been used to encourage syphilis counselling and testing among
189 MSM in clinics^{4,62}.

190

191 **3.2.3 Patient-level interventions**

192 Syphilis screening strategies at the patient level have included internet and text-message
193 assisted strategies to regularly remind patients to initially screen⁶³ or retest for syphilis⁶⁴.

194 Encouraging results from these two studies support the use of text messages for promoting
195 syphilis testing. Monetary incentives have been used to improve testing for HIV and other
196 STIs^{65,66}, including syphilis testing⁶⁶. The syphilis test incentive study offered individuals with
197 drug addiction or unstable housing small rewards for obtaining their syphilis results or
198 seeking treatment if required⁶⁶. Further research is needed to assess the cost-effectiveness
199 for providing financial incentives to increase syphilis testing uptake.

200

201 **3.3 Non-clinic and community based testing strategies**

202 Although screening for syphilis to date has primarily been conducted in clinic-based settings
203 ^{10,67}, advances in STI diagnostics have increased the number of non-clinic and community-
204 based settings where syphilis testing is feasible^{12-14,68}. Advantages of non-clinic and
205 community-based testing include reaching individuals who may not seek clinical services,
206 and integrating testing within existing community-based services in collaboration with local
207 partners. Community-based syphilis testing strategies for key populations through outreach
208 at entertainment or commercial sex venues and mobile testing units have proven to be
209 effective in reaching key populations^{31,69}. These testing approaches have been integrated
210 into routine STI surveillance systems⁷⁰. Furthermore, internet and social network based
211 testing and promotion have been used to scale up earlier diagnosis of syphilis in key
212 populations⁷¹⁻⁷³.

213

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

218

219 **3.3.1 Venue-based syphilis testing**

220 Universal screening for syphilis has been provided in jails and other correctional settings in
221 several countries^{50,69,74-76}. Success of the venue-based strategy depends on the local
222 epidemiology of syphilis. Data from STI screening conducted at correctional facilities in the
223 United States suggests a high syphilis prevalence in the incarcerated populations, and
224 programs have been particularly successful for identifying syphilis outbreaks in
225 heterosexuals⁷⁶⁻⁸⁰. Although syphilis testing in correctional facilities introduces a range of
226 special challenges, it also provides unique opportunities for expanding syphilis testing^{50,75}.

227

228 Similarly, routine screening of syphilis in PWUD have been conducted at drug use
229 rehabilitation and treatment facilities, including methadone maintenance treatment (MMT)
230 clinics and syringe exchange programs in a few countries⁸¹⁻⁹⁰. For example, syphilis
231 screening is integrated into the national drug rehabilitation system as a standard medical
232 service for PWUD in China^{87,91}. PWUD receiving MMT are routinely screened for syphilis
233 together with HIV and HCV⁸⁷. Findings demonstrated the feasibility and cost-effectiveness of
234 integrating syphilis screening into existing PWUD programs^{87,88}.

235

236 **3.3.2 Mobile testing sites**

237 Mobile STI screening programs are particularly well suited for populations in rural, low-
238 income communities or areas with disproportionately high syphilis burden⁹²⁻⁹⁵. Mobile van
239 testing services have successfully provided services at community events (e.g. Gay Pride
240 parades and parties) or at sex/entertainment venues where higher risk sex often takes
241 place⁹⁶. Mobile vans have also been used to deliver syphilis testing services to target high

242 risk populations in other developing and developed countries, such as Russia^{93,97-100}, Peru¹⁰¹
243 and Guatemala¹⁰². This research suggests that mobile testing units effectively expand first-
244 time syphilis testing among a subset of key populations that do not access clinical services
245 ^{95,96,102}.

246
247 Periodic outreach syphilis testing services have been conducted at entertainment or sex
248 venues, for example, brothels, gay bars, bathhouses. These programs have increased
249 syphilis testing among PWUD^{81,98,103-105, 106-108}, MSM^{31,51,109-111} and transgender people¹¹².
250 For example, health outreach teams in two Chinese cities offered free onsite rapid
251 syphilis testing to approached at various types of commercial sex venues¹⁰⁷. Among the
252 FSW who were offered rapid syphilis testing, 95% accepted the test; 7% tested positive,
253 among which 75% agreed to visit an STI clinic for confirmatory testing, and 66% were
254 willing to notify their partners of the test result¹⁰⁷.

255

256 ***3.3.3 Use of new communication technologies to increase syphilis testing***

257 We define new communication technologies as mass communication using digital
258 technologies such as social networking platforms. Public campaigns through targeted
259 messaging interventions have been used to increase syphilis knowledge and testing. These
260 programs have focused on MSM and transgender people^{110,113,114}. Mixed findings were
261 reported. For example, a syphilis awareness public campaign targeting MSM in eight U.S.
262 cities using social marketing approach reported an increased awareness of syphilis in some
263 cities and increased syphilis testing associated with campaign participation¹¹³. However, the
264 “Check Yourself “public campaign conducted in Los Angeles in the U.S. did not find a
265 significant association between campaign awareness and syphilis testing in MSM¹¹⁴. Among

266 technology-focused testing strategies, crowdsourcing is another approach to developing
267 new syphilis testing campaigns. Crowdsourcing is the process of having a group solve a
268 problem and then sharing the solution with the public.¹¹⁵ Crowdsourcing has been used to
269 solicit novel content for promotional images, videos, and HIV testing strategies. A stepped
270 wedge trial randomized controlled trial evaluating this approach is underway and includes
271 syphilis testing as a secondary outcome¹¹⁶. Cross-sectional data from this study suggested
272 that dual HIV/syphilis self-testing promoted through the internet could be a feasible
273 approach for increasing syphilis testing among MSM¹¹⁷.

274

275 There is a small but growing literature that examines the internet as a platform for
276 distributing syphilis test kits, self-collection kits, or non-clinical testing^{15,118-121}. Two pilot
277 studies allow MSM to download a referral letter for presentation at a testing laboratory for
278 a syphilis test; then results were received online^{122,123}. However, both sites found that fewer
279 than 10% of those who requested a letter received a test kit^{122,123}. Other studies have
280 examined new technologies as tools to promote syphilis testing^{15,16,124-126} including using
281 Facebook and Twitter^{124,125}; online research surveys on gay websites^{15,16}. However, linkage
282 to clinic-based syphilis testing from banner advertisements was less than 20% in both
283 studies that measured it^{15,16}. A study which evaluated the effect of a social network-based
284 campaign on STI testing use in youths reported a significant increase in syphilis testing (from
285 5% to 19%, pre- and post-campaign)¹²⁴. Another study evaluating automated text message
286 and email reminders promoting syphilis re-testing among MSM increased detection of
287 syphilis⁶³.

288

289 **4. EXPERT COMMENTARY**

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

311

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

313

	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	15,63,110,111,3,114,124-126,133			134,135

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

315

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

324

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

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

335

336 While existing studies showed that non-clinic based programs were effective in improving
337 the access of key populations to syphilis screening services, particularly among those who
338 were more hidden and had higher STI risks^{12,69,142}, few studies have evaluated linkage to
339 care and related services. The gap between testing and treatment services could
340 compromise the effectiveness of these strategies¹⁴³. In addition, advances in new syphilis
341 testing approaches have yet to translate into clinic seeking and clinic service uptake. Lessons
342 can be learnt from the larger HIV new communications technology literature when
343 designing new syphilis testing strategies¹⁴⁴.

344

345 **5. FIVE-YEAR VIEW**

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

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

354

355 **6. KEY ISSUES**

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

372

373 **7. CONCLUSION**

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

379

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