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Characteristics of gay, bisexual and other men who have sex with men with multiple diagnoses of infectious syphilis in British Columbia, Canada, 2005-2014

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32

33

34 **Short Summary (<30 words):** A descriptive study of individuals with ≥ 4 syphilis diagnoses in BC, Canada,
35 demonstrated a group of MSM living with HIV; approximately half could be linked through sexual or
36 venue-based networks.

37

38 **Abstract (max 250)**

39 Background: Infectious syphilis has increased substantially over the past decade. Targeting limited public
40 health resources towards subpopulations with multiple re-infections may have a large impact in
41 reducing onward transmission within a community.

42 Methods: A chart review was conducted for individuals with ≥ 4 infectious syphilis diagnoses between
43 2005 and 2014 (the top 1% of all syphilis diagnoses in British Columbia, Canada). We characterized the
44 socio-demographics, partner notification outcomes and social network.

45 Results: Between 2005 and 2014, there were 30 individuals with ≥ 4 syphilis diagnoses, accounting for
46 139 diagnoses. All were men who have sex with men and 29 (96%) were HIV-positive. Of the 139
47 diagnoses, 65% occurred in the early latent stage of infection, 22% in the secondary stage and 14% in
48 the primary stage. The median number of sexual partners per diagnosis was five (range=1-50). Among
49 the 838 partners reported, 79% were notifiable, 53% were notified and 23% were reported to be tested
50 and/or treated. Sexual network mapping showed that almost half of the members of this group could be
51 linked to one another either directly or indirectly via partners over ten years. Social network mapping
52 demonstrated high connectivity, with four venues associated with almost two-thirds of the study
53 population.

54 Conclusion: The connectivity and recurrent diagnoses in this study population suggest potential benefits
55 of targeted interventions to individuals with multiple diagnoses and their partners. Our study highlights
56 the need for enhanced care, increased syphilis testing frequency, and exploring alternative preventative
57 methods among individuals with syphilis re-diagnoses to reduce syphilis incidence.

58 **Key Words:** syphilis; repeat diagnoses; gay, bisexual and other men who have sex with men; sexual
59 network; partner notification outcomes

60

61

62 INTRODUCTION

63 Infectious syphilis rates have been increasing in many high-income countries including Canada, United
64 States, and Europe,(1-3), driven predominantly by diagnoses among gay, bisexual, and other men who
65 have sex with men (MSM).(1-3) In British Columbia (BC), syphilis notifications nearly doubled from 6.8 to
66 11.9 per 100,000 between 2005 and 2014, with MSM accounting for 71% of diagnoses.(4) Decreased
67 condom use, changes in risk perceptions and increased testing have been suggested as contributing
68 factors to the increasing rates.(5,6)

69 The increase in syphilis incidence is particularly challenging in the context of limited and even decreasing
70 public health resources.(7,8) Thus, there is a need to target and prioritize public health services to those
71 most likely to benefit. Studies have shown that individuals with re-infections are part of larger sexual
72 networks, have higher transmission rates, and are at increased risk of re-infection compared to
73 individuals with single infections.(9-11) In fact, some jurisdictions have syphilis epidemics with high
74 proportions of syphilis re-infections.(12) Factors associated with syphilis re-infection include HIV co-
75 infection, substance use and the stage of syphilis infection (i.e. secondary or early latent).(12-17) These
76 findings support the notion that individuals with multiple syphilis infections may belong to densely
77 connected high-risk sexual networks.(15,17) Interventions targeted at these networks may be an
78 effective strategy to controlling syphilis.(18,19)

79 Here, we characterized the socio-demographics, partner notification (PN) outcomes and social networks
80 of individuals with a high number of repeat syphilis diagnoses in order to inform public health
81 interventions.

82

83 METHODS

84 *Syphilis investigation*

85 Current Canadian guidelines recommend risk-based syphilis screening. Specifically for MSM, those who
86 report unprotected sex in the preceding year are recommended to be screened for syphilis and other
87 STIs(20). Additionally in BC, people living with HIV (PLHIV)are recommended to be screened annually or
88 every 3-6 months if they report risk behaviours or symptoms,(21) which have been in place since 2011
89 (personal communication, Dr. Rolando Barrios).

90 In BC, syphilis laboratory testing, case follow-up and counselling, and epidemiological data collection
91 and analysis are centralized at the BC Centre for Disease Control (BCCDC), yielding a complete census of
92 all cases. From 2005-2014, the syphilis screening algorithm consisted of rapid plasma regain (RPR) first
93 and if reactive, a treponemal test (usually *Treponema pallidum* particle agglutination test [TPPA]). If
94 TPPA is weakly positive, then a secondary treponemal test (e.g. line immunoassay) was used to confirm
95 the diagnosis. Clinicians could also use dark field microscopy or submit a sample for nucleic acid
96 amplification testing to diagnose syphilis.

97 All positive syphilis results are reviewed by a team of expert STI physicians who assess, diagnose, stage,
98 and recommend treatment based on historical syphilis test results and in consultation with the testing
99 provider and/or patient. Case definitions for infectious syphilis (i.e. primary, secondary, or early latent
100 stages) are described in our routine surveillance report.(4)

101 Nurses at the BCCDC (“syphilis nurses”) follow-up all syphilis cases in BC who systematically collect
102 details on demographics, risk factors (e.g. MSM), and HIV co-infection (including HIV viral load since
103 2008). Syphilis nurses also perform or coordinate PN (the process of identifying, informing, testing and
104 treating sexual partners who are potentially exposed to syphilis) to prevent transmission and minimize
105 complications of infections.(22) Information on syphilis cases and their partners are recorded in the STI
106 Information System (STI-IS), the provincial STI database, which includes information on all reportable
107 STIs (i.e. chlamydia, gonorrhoea, and syphilis).

108 The trace back period for PN is 3 and 6 months plus duration of symptoms for primary and secondary
109 syphilis, respectively, and 12 months for early latent syphilis. PN can be completed by the case (i.e. index
110 referral) or by a healthcare provider (such as the testing provider, syphilis nurse or other public health
111 nurse, i.e. provider referral). If the case preferred to do his/her own PN or another provider completed
112 the PN, the syphilis nurse follows-up with the case or provider to ensure PN occurred and records this
113 information in the index case’s and/or the partner’s chart. A partner chart is created when the syphilis
114 nurse is able to reach the partner and verify at least two personal identifiers (e.g. name and date of
115 birth).

116 *Data sources*

117 Using STI-IS, all individuals in BC with infectious syphilis diagnoses between January 1, 2005 and
118 December 31, 2014 (the study period) were identified. Data specific to each diagnosis was extracted
119 (age, gender, ethnicity, region of residence, stage of syphilis infection, HIV status at time of diagnosis,
120 and viral load in the three months prior to syphilis diagnosis, when available). Also, any chlamydia,
121 gonorrhoea or infectious syphilis diagnoses from inception of the database (1998) to 2014 were obtained
122 for these individuals. STI co-infections (chlamydia or gonorrhoea) were defined as a diagnosis within a
123 one-month window of the syphilis diagnosis date. History of an STI (chlamydia, gonorrhoea or syphilis)
124 was defined as ever having had a diagnosis prior to one-month before the syphilis diagnosis date.

125 A chart review was conducted to determine PN outcomes and create sexual and venue based network
126 maps for each diagnosis among individuals with four or more syphilis diagnoses during the study period.
127 A cutoff of four was chosen as they represented the top 1% of individuals diagnosed with syphilis during
128 our study period and may represent a core group, similar to the rationale for a study of syphilis re-
129 infections.(12) We collected information on the total number of partners, number of notifiable partners,
130 number of notified partners, and number of partners tested/treated. Anonymous partners were those
131 whose identity was unknown to the case. ‘Tested/treated’ were combined as BCCDC guidelines
132 recommend treating sexual partners exposed within 90 days of diagnosis and/or symptom onset
133 regardless of test results.(23) Where possible, we assessed partner outcomes, specifically any syphilis

134 diagnoses and HIV status during the study period. We also collected information about venues for
135 seeking or meeting sexual partners, including online sites.

136 *Analyses*

137 Descriptive statistics were used to describe individual- and diagnosis-specific characteristics. Chi-square
138 or Fisher's exact tests were used to compare categorical variables and Kruskal-Wallis test to compare
139 medians. Statistical significance was set at $p < 0.05$. Data was analyzed using SAS 9.4 software (Cary, NC).

140 Two network maps were developed. A sexual network map included all sexual partners of syphilis cases
141 (i.e. four or more syphilis infections between 2005 and 2014), including anonymous partners during the
142 study period. In this map, a partner's unique STI-IS identifier was used to make linkages with other cases
143 and partners. A second map focused on social networks and described reported venues for meeting
144 sexual partners or engaging in sex. Social network mapping was conducted through Pajek 4.04
145 (Ljubljana, Slovenia).

146 *Ethics*

147 This work was completed to support the surveillance for the provincial syphilis epidemic response under
148 BCCDC's public health mandate. Thus, ethics approval was not required.

149

150 **RESULTS**

151 Between 2005 and 2014, there were 3285 cases of infectious syphilis diagnoses among 2720 unique
152 individuals. Fifteen percent (412/2720) had more than one syphilis diagnoses: 305 (11%) had two, 76
153 had three (3%) and 30 (1%) had four or more diagnoses which together, accounted for 30% (977/3285)
154 of all syphilis diagnoses in BC during the study period.

155 Thirty individuals had four or more syphilis diagnoses during the study period (range: 4-8) for a total of
156 139 diagnoses. All 30 individuals were MSM, 24 (80%) self-reported as Caucasian and 28 (93%) were
157 HIV-positive at their earliest syphilis diagnosis. One individual seroconverted between their earliest and
158 latest syphilis diagnosis. At the time of their earliest diagnosis, all cases but one resided in the Greater
159 Vancouver area. Mean age of cases was 41.2 years (standard deviation [SD]: 7.4) and 47.3 years (SD: 7.5)
160 at earliest and latest diagnosis, respectively. At the time of the earliest diagnosis, 14 (47%) had at least
161 one prior chlamydia or gonorrhea infection (Table 1).

162 Among the 139 diagnoses, 90 (65%) were diagnosed in the early latent stage, 30 (22%) in the secondary
163 stage and 19 (14%) in the primary stage. The proportion of syphilis diagnosed in the primary or
164 secondary stage generally decreased from 47% to 30% from the first to the fourth diagnoses,
165 respectively. Eight diagnoses (6%) had a concurrent chlamydia or gonorrhea infection. HIV viral load
166 data was available starting in 2008. Ninety-five (89%) of the 107 diagnoses among HIV-positive cases
167 had their viral load measured at the time of syphilis diagnosis. Viral load was undetectable in 66% of the
168 diagnoses (Table 1).

169 The time from one diagnosis to the subsequent diagnosis was calculated, yielding 109 intervals. Forty-
170 two (39%) intervals were less than 365 days. The median interval between syphilis diagnoses was 452
171 days (interquartile range [IQR]: 288-787 days).

172 *Partner notification outcomes*

173 PN details were available for 111 of the 139 diagnoses (Table 2). Overall, 838 partners were reported, of
174 which 667 (79%) were notifiable, 440 (53%) were notified and 191 (23%) were tested and/or treated.
175 The median number of sexual partners reported per diagnosis was 5 (IQR: 2-11). The median number of
176 sexual partners did not differ significantly among the three stages of infection ($p=0.21$, results not
177 shown).

178 Out of all 139 diagnoses, 38 (27%) reported at least one anonymous partner, representing at least 171
179 anonymous partners. Multiple investigations reported “multiple” anonymous partners without a specific
180 number and were not included in any further PN outcomes or networks.

181 The index cases assumed responsibility for their own PN in 35% of the investigations; this increased over
182 the study period, from 14% (4/28) in 2005-2007 to 23% (8/35) in 2008-2010 to 47% (36/76) in 2011-
183 2014. A higher proportion of partners were notifiable ($p<0.01$) by index referral when compared with
184 provider referral. The proportion of partners notified or tested/treated did not statistically differ (Table
185 2).

186 Over these three time periods, the proportion of partners notified increased from 29% in 2005-2007 to
187 47% in 2008-2010 and lastly 68% in 2011-2014 ($p<0.01$), while the proportion of partners tested/treated
188 remained similar.

189 *Sexual and social networks*

190 Figure 1 depicts the sexual network of the 30 cases and 811 unique partners (i.e. excluding duplicates or
191 the study cases reported as partners) over the 10-year span. The largest cluster linked 390 partners and
192 10 cases, and represented 48% of the network. The second largest clusters linked 92 partners and 4
193 cases, representing 11% of the network.

194 Twenty-two (74%) cases and 43 (32%) diagnoses had recorded data on venues or sites where sexual
195 encounters occurred or sexual partners were met. While the majority of venues/sites were specifically
196 named, types of venues were also reported (e.g., bathhouse, bars). Online dating sites and bathhouses
197 were most commonly reported, by 19 and 12 cases, respectively. Figure 2 shows a network map
198 between 19 cases and the specifically named venues/sites. The network highlights two online dating
199 sites (depicted as a blue triangle) reported by 7 and 5 cases, along with two physical venues (depicted as
200 green triangles) reported by 4 cases each (Figure 2).

201 *Partner characteristics*

202 Of 811 unique partners reported, 123 individuals had a STI-IS identifier recorded in the index case's
203 chart. Two STI-IS identifiers were invalid, yielding 121 partners that were included in this analysis. During

204 the study period, 51 (43%) partners had at least one syphilis diagnosis. These 51 partners accounted for
205 84 diagnoses between 2005 and 2014. Repeat diagnoses were seen for 25 (50%) of these contacts.
206 Specifically, 17 (33%) and 8 (16%) had two and three infections within the study period, respectively.
207 Among those with a syphilis diagnosis, all were MSM and 43 (84%) were HIV-positive. One person
208 declined testing and 7 were HIV-negative. No differences in HIV status or STI diagnoses were identified
209 between partners reported by cases included in the two largest sexual network clusters and those
210 reported by cases outside these two clusters (Chi-Square, $p > 0.05$, results not shown).

211

212 **DISCUSSION**

213 Our review of individuals with four or more syphilis diagnoses demonstrated a group of MSM of which
214 the majority were HIV-positive and half had a history of another STI at their earliest diagnosis. Most
215 were diagnosed in the early latent stage of infection and of those who were living with HIV, about two-
216 thirds had an undetectable viral load around the time of the syphilis diagnosis. Approximately half of
217 these individuals could be linked through sexual and venue-based networks.

218 One study in Belgium of individuals with five or more syphilis diagnoses over a 20-year period reported
219 similar findings, with all individuals being MSM, HIV-positive, and on antiretroviral therapy.(12) Similarly,
220 other studies that used varying definitions of repeat infection, including 2 or more syphilis diagnoses
221 within a 3-, (16,24) 4-, (13) 5-, (25), or 12-year period (14), reported MSM and HIV co-infection were
222 common among those with repeat infection.

223 Almost two-thirds of the diagnoses in our study population occurred in the early latent stage, similar to
224 other studies.(12,13) The large proportion of diagnoses in this asymptomatic early latent stage of
225 infection may suggest that this group is routinely testing for syphilis, potentially as part of HIV care.(21)
226 However, diagnosis in the early latent stage of infection may also suggest a potentially long period of
227 infectiousness increasing the risk of transmission. Interventions aimed at increasing the frequency of
228 syphilis testing and raising awareness of signs and symptoms in individuals with repeat diagnoses have
229 been suggested as a particularly effective strategy to control syphilis (26) and new testing modalities like
230 online testing services being implemented in BC, the 'GetCheckedOnline' program, could help improve
231 accessibility to syphilis testing.

232 The majority of our study population were HIV-positive, on antiretroviral therapy, and virologically
233 suppressed. This suggests this group is engaged in routine HIV care and achieving viral suppression,
234 reducing HIV transmission potential. However, given that most partners were similarly HIV co-infected
235 and many had multiple syphilis diagnoses during our study period, seroadaptive behaviour (i.e. choosing
236 partners who have the same HIV serostatus) and condomless sex may play a role in the transmission of
237 syphilis in this network.(27,28) While enhanced counseling and education may be beneficial, re-
238 diagnoses among our study population and their partners and history of other STIs suggest ongoing
239 sexual behaviours putting them at risk for STIs. Therefore, other strategies like a biomedical
240 preventative measure may be an appropriate and effective intervention to reduce subsequent STIs, as
241 shown in a recent pilot study of doxycycline prophylaxis.(29) Two similar pilot studies of doxycycline

242 prophylaxis are underway in BC, led by local researchers and members of our BCCDC team. If effective,
243 this may be an intervention that can prevent syphilis acquisition and transmission within this sexual
244 network.

245 Our study population reported a median of five partners per syphilis diagnosis, compared with three in a
246 previous study of a random sample of syphilis cases among MSM in BC,(30) suggesting this group is part
247 of dense sexual networks. Half of partners reported by our study population were not notified, partly
248 due to incomplete partner information and/or anonymous partners. While this finding is similar to our
249 previous study,(30) improving engagement of this group and their partners may be a particularly
250 important strategy to control syphilis given the infectiousness of syphilis and our finding of high
251 connectivity in this network. Indeed, over 40% of partners whose outcomes were known were
252 diagnosed with syphilis or almost 10% of all partners reported, higher than in our previous study.(30)

253 Finally, our analysis found two networks that linked almost half of the cases, despite limitations of self-
254 reporting, recall bias, and anonymous or incomplete partner information. Several networks were linked
255 by only a few partners who may be equally important contributors, particularly if they are not being
256 tested and/or treated as frequently. Together, the cases and their partners accounted for 223 or 7% of
257 all syphilis diagnoses in BC in the study period demonstrating the disproportionate burden of syphilis
258 infections borne by a small group of individuals. Thus, enhanced public health resources towards this
259 group and their networks can have a large impact in the overall syphilis epidemic.

260 Venue-based network analyses can help complement PN by identifying spaces that may be associated
261 with higher risk of syphilis transmission.(31S) We found four venues that linked almost two-thirds of our
262 cases in the venue-based network. Targeting these venues to communicate public health messages and
263 access to syphilis testing, such as on-site testing, may help reach this network.

264 Notably, our network diagram was depicted in a compressed format over the 10-year period and does
265 not show the dynamic and evolving nature of partnerships over time. We have begun to systematically
266 collect partner information to better understand networks that may be driving the syphilis epidemic,
267 such as partners who may be important bridges between high-risk individuals.

268 A strength of our study is that it encompasses the entire BC population over a long period of time.
269 However, by requiring a set number of diagnoses within a set period, there is a bias towards individuals
270 who remained in BC for a sufficient period of time to acquire infections and be diagnosed as well as
271 those that test more frequently. Also, we may have missed individuals who moved out of BC after their
272 initial syphilis diagnosis. Nevertheless, the persistence of the group over a long period of time suggests
273 that this is a stable group (10) and that targeting individuals with multiple syphilis infections and their
274 networks could have a significant influence on rates of syphilis in the community. Another concern is the
275 potential for misclassification of treatment failure and a syphilis re-diagnosis. However, due to the
276 centralization of syphilis data and the review of each diagnosis by a small number of syphilis physicians,
277 this misclassification is likely minimal. Additionally, our network depictions were subject to recall bias,
278 missing, incomplete, or anonymous partner data and thus only represented a partial network. Lastly,
279 routine or more frequent syphilis testing could have led to the higher number of diagnoses among this

280 group. We have found a higher proportion of syphilis diagnosed in the early latent stage among PLHIV,
281 which may reflect more frequent screening.

282

283 **CONCLUSION**

284 Our study found that focusing on persons with syphilis re-infection can be a useful approach to
285 identifying networks engaged in high risk sexual behaviour. Characterizing these networks can target
286 public health resources to individuals most likely to benefit from enhanced care and counselling, syphilis
287 testing, and potential biomedical methods to prevent re-infection and reduce onward syphilis
288 transmission.

289

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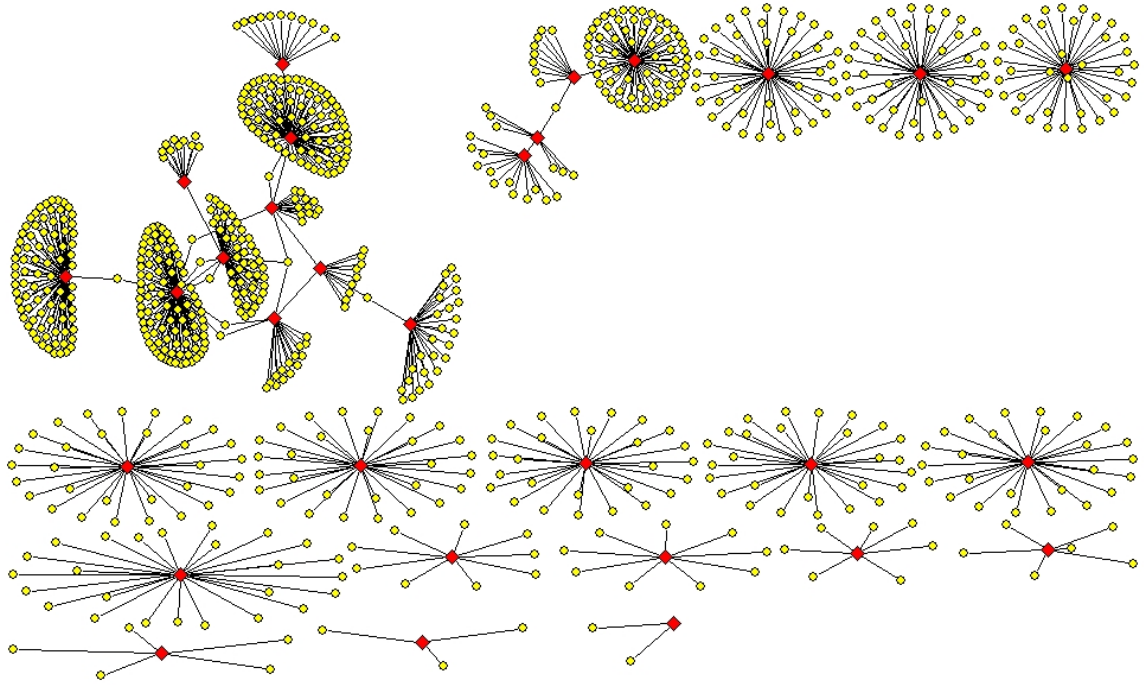
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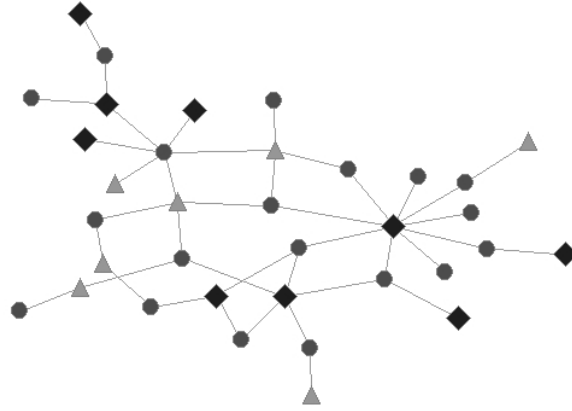
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Figure 1. Compressed sexual network of individuals with ≥ 4 syphilis diagnoses in British Columbia, 2005 to 2014



Legend: Cases (red diamonds), partners (yellow circles)

Figure 2. Compressed social network of venues and dating sites of individuals with ≥ 4 syphilis diagnoses in British Columbia, 2005 to 2014



Legend: Cases (circles), physical venues (triangles), online sites (diamonds)

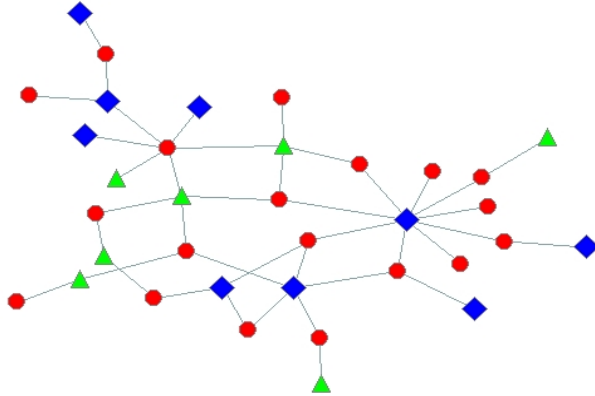


Table 1. Demographic and clinical characteristics of cases with ≥ 4 syphilis diagnoses, 2005-2014

Individual based characteristics (n=30)	
	n (%)
Age (years), Mean (IQR)	
At earliest diagnosis	41.2 (36-47)
At latest diagnosis	47.3 (43-52)
Caucasian	24 (80.0)
MSM	30 (100.0)
HIV Status – at earliest diagnosis, latest diagnosis	
HIV-positive	28 (93.3), 29 (96.7)
HIV-negative	1 (3.3), 1 (3.3)
Unknown	1 (6.7), 0 (0)
History of STI – at earliest diagnosis	
Chlamydia	5 (16.7)
Gonorrhoea	9 (30.0)
Syphilis	5 (16.7)
Any STI	15 (50.0)
Diagnoses based characteristics (n=139)	
Year of diagnosis	
2005-07	28 (20.1)
2008-10	35 (25.2)
2011-14	76 (54.7)
Syphilis stage	
Primary	19 (13.7)
Secondary	30 (21.6)
Early latent	90 (64.7)
STI Co-infection	
Yes	8 (5.7)
No	131 (94.3)
Viral load (n=107)*	
Undetectable (<40 copies/mL)	71 (66.4)
41-399 copies/mL	8 (7.5)
400-999 copies/mL	5 (4.6)
1000-9999 copies/mL	2 (1.9)
$\geq 10,000$ copies/mL	9 (8.4)
Unknown	12 (11.2)

IQR=interquartile range

*Viral loads at the time of syphilis diagnoses, among HIV-positive individuals, which became available in 2008.

Table 2. Partner notification outcomes per diagnosis for individuals with four or more syphilis diagnoses in British Columbia, 2005-2014 (n=111)

	Number of Partners	Number of Notifiable Partners	Number of Partners Notified	Number of Partners Tested/Treated*
Median (IQR)	5 (2-11)	3 (1-8)	2 (1-5)	1 (0-2)
Mean	7.6	6.0	3.9	1.7
Range	1-50	0-50	0-30	0-15
PN Outcomes Over Time				
2005-2007	192	165 (86%)	55 (29%)	46 (24%)
2008-2010	254	181 (72%)	120 (47%)	53 (21%)
2011-2014	392	321 (82%)	265 (68%)	92 (23%)
PN by Referral Group				
Index Referral	385	359 (93%)	247 (64%)	46 (12%)
Provider Referral	453	308 (68%)	193 (43%)	145 (32%)
Total Number (%)	838	667 (79%)	440 (53%)	191 (23%)

*Includes self-reported outcome by contact or index case.

IQR=interquartile range, PN = partner notification