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The Swiss STAR trial – an evaluation of target groups for sexually transmitted infection screening in the sub-sample of men

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Summary

OBJECTIVES: In Switzerland, universal health insurance does not cover any routine testing for sexually transmitted infections (STIs), not even in individuals at high risk, and extra-genital swabbing is not standard of care. We determined the prevalence and incidence of human immunodeficiency virus (HIV), viral hepatitis and non-viral STIs in a multicentre prospective observational cohort of multi-partner men who have sex with men (MSM) and other men.

MATERIALS AND METHODS: Between January 2016 and June 2017, we offered free STI testing to all men with multiple sexual partners (three or more in the previous 12 months), with follow-up examinations every 6 months. We used multiplex polymerase chain-reaction testing (for *Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis, Mycoplasma genitalium*) on pooled swabs (pharynx, urethra/vagina, anus), and antibody tests for HIV and *Treponema pallidum* at every visit, and for hepatitis B/C at baseline.

RESULTS: We screened 779 multi-partner MSM and 92 other men. Previously undiagnosed HIV was found in 0.5% vs 0.0%, respectively and *T. pallidum* antibodies in 15.3% vs 1.1%. STIs requiring antibiotic treatment comprised: active syphilis 1.7% vs 0.0%; *N. gonorrhoeae* 10.3% vs 0.0%; *C. trachomatis* 8.7% vs 1.1%. One in four MSM versus 1 in 100 other multi-partner men had any of these three STIs at baseline. 10.4% vs 1.3% had a history of hepatitis B, 31.9% vs 47.3% had no immunity (HBs-AB <10 IU/l). Ten MSM had HCV antibodies (1.4%), with 8 out of the 10 being MSM with HIV; HCV seroprevalence was 0.3% among HIV-negative MSM. In MSM, incidence of the three bacterial STIs was 25.5 per year over 333 person years of follow-up, HIV incidence was 0.3%. Non-condom-use (in the last 3 months) for anal/vaginal sex was not associated with STIs. Independent risk factors were sex with men (adjusted odds ratio [aOR] 16.4) and the number of sexual partners (aOR 2.3 for >20).

CONCLUSION: Among MSM, but not among other multi-partner men, STIs, mostly asymptomatic, are common. Given the high risk of onward transmission, low-cost or free routine screening of multi-partner MSM is a public health priority.

Keywords: *sexually transmitted diseases, men, sexual and gender minorities, hepatitis C, hepatitis B, HIV, homosexuality, sexual behaviour*

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Editorial note

We decided to publish the main results of the Swiss STAR trial as two separate publications – one on the sub-sample of men, another on the sub-sample of women. Reasons for this include anatomical and epidemiological differences, and the medical disciplines in charge: urology and infectious diseases for men, and gynaecology for women. Furthermore, the two main target groups, men who have sex with men and female sex workers, differ with respect to the legal and societal context of sexual contacts, all of this probably resulting in distinct readerships. The detailed joint methods for both publications are available as online supplement.

Four key messages

1. In Switzerland five multi-partner MSM need screening for bacterial STIs to find one with a notifiable and clinically relevant infection: syphilis, gonorrhoea, or chlamydia.

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2. Biannual STI screening among multi-partner MSM, regardless of condom use, should be offered as part of a free/low-cost package that also includes an HIV test.
3. In Switzerland, multi-partner men who only have sex with women will not benefit from STI screening in the absence of symptoms, or from regular routine HIV testing.
4. In Switzerland, hepatitis C prevalence among non-HIV-diagnosed MSM is low with no evidence for an increasing trend.

Introduction

The Swiss National Programme on human immunodeficiency virus (HIV) and other sexually transmitted infections (STIs) 2011–2017 highlights the importance of early detection and correct treatment of STIs in addition to behavioural changes and vaccinations, where applicable [1]. Reducing numbers of sexual partners is a behavioural change that likely results in a decreased risk of STIs [2], although the role of condom use to prevent syphilis and gonorrhoea, and particularly chlamydia, has been debated [3–6].

The Swiss healthcare system, however, is a substantial barrier to the implementation of this recommendation as universal health insurance does not cover any routine testing for STIs, even in individuals at high risk. Although individuals with symptoms of an STI are likely to contact a physician to receive appropriate treatment, asymptomatic individuals may be reluctant to do so, since the costs for STI screening have to be paid out of their own pocket. If Swiss published recommendations are closely followed and swabs from different anatomical sites are not pooled [7], testing costs for syphilis, gonorrhoea, and chlamydia add up to more than US$ 700 or, when adjusted for purchasing power parity, of almost US$ 600 PPP [8]. Since this characteristic of the Swiss healthcare system hinders the implementation of a diagnostic procedure in the interest of public health, the Swiss government is currently investigating the implementation of a new financing system for such diagnostic procedures. However, to establish a system for the financing of these tests, the ideal target group/s for such a diagnostic procedure need to be defined.

The prevalence and incidence of STIs in clients of testing sites in Switzerland is largely unknown. The primary objective of the STAR trial was to describe the prevalence of HIV and common non-viral STIs across different behavioural/demographic risk categories. Although routine testing for hepatitis C virus (HCV) in men who have sex with men (MSM) without known HIV infection is not recommended in Switzerland, studies have recommended close monitoring of trends in the spread of HCV among MSM [9]. For this reason, we included testing for HCV antibodies as a secondary objective for MSM and female sex workers (FSWs). Other secondary objectives were to describe the incidence of infections with HIV and common non-viral STIs in MSM and FSWs, the prevalence of chronic hepatitis B, and to compare self-reported with actual hepatitis B vaccination status / immunity. We aimed to determine prevalence and incidence of HIV and STIs in two groups considered at high risk for STIs: FSWs [10] and MSM. This paper presents the results for MSM and a small comparison group of multi-partner men who exclusively had sex with women.

Materials and methods

Across Switzerland, between January 2016 and June 2017, we offered free STI testing to men and women with multiple sexual partners (three or more in the last 12 months) attending multiple STI testing sites. The study provided follow-up examinations every 6 months. We used multiplex polymerase chain-reaction testing (PCR) (for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Mycoplasma genitalium*) of pooled swabs (pharynx, urethra/vagina, anus), and antibody tests for HIV and *Treponema pallidum* (IgG/M, plus rapid plasma reagin if positive) at every visit, and for hepatitis B and C at baseline. At every visit, participants self-completed an anonymous online questionnaire. The detailed methods are described in appendix 1.

Ethical approval was given on 21 July 2015 by the lead ethics committee Eastern Switzerland (EKOS) under BASEC PB_2016-00738, and subsequently approved by ethics committees in Bern (KEK BE), Basel (EKNZ), Vaud (CER-VD), and Zurich (KEK ZH).

Results

We enrolled 779 MSM (including 29 male sex workers) and 92 other multi-partner men who reported sex exclusively with women. Enrolment of male participants peaked in summer 2016. Overall, 535 men returned at least once for follow up, resulting in a follow-up rate of 61% and 338.0 person-years of follow-up. All participants received all HIV/STI tests; five men were not tested for HBV, and for 55 MSM HCV-RNA could not be determined because one centre used the wrong sampling tubes; they were excluded from the respective analyses.

Sociodemographic characteristics

Participants from the French-speaking part of Switzerland were over-represented. Most participants were recruited in dedicated MSM health centres (‘Checkpoints’). Among MSM, 0.3% were transgender men, 3.7% had sold sex since their last HIV test and 3.6% had HIV diagnosed prior to enrolment. Median age was 33 years for MSM vs 32 years among other multi-partner men. Nationality broadly reflected the composition of the Swiss general population. Almost all had health insurance in Switzerland. Almost half of MSM and about a third of other men were single. Table 1 shows the sociodemographics.

Risk/precautionary behaviour

Overall, 78% of MSM vs 84.2% of other multi-partner men reported full vaccination against hepatitis B. Human papilloma virus (HPV) vaccination was reported by 4.1% vs 1.4%, and in men under 27 by 8.3% vs 6.7%.

A history of previously diagnosed STIs was reported by 44.2% of MSM vs 17.4% of other multi-partner men. Furthermore, 43.0% vs 10.9% had more than 10 partners in the past 12 months; sex in a group was reported by 40.5% vs 9.8%. Among MSM, two thirds had met at least half of their partners online and 6.5% had paid for sex since their

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Table 1: Overview and sociodemographic parameters, risk and precautionary behaviours at baseline.

		MSM n/N (%)	Other men n/N (%)
Study recruitment overview			
Persons with baseline visit		N = 779	N = 92
Persons with follow-up visits		n = 526	n = 9
Follow up visits		n = 623	n = 9
Follow-up rate		526/779 (67.5)	9/92 (9.8)
Person years of follow up		333.2 years	4.8 years
Location of VCT centre in Switzerland	French-speaking part	373/779 (47.9)	3/92 (3.3)
	German-speaking part	406/779 (52.1)	89/92 (96.7)
Service recruited at	Dedicated MSM health centre	593/779 (76.1)	4/92 (4.3)
	General hospital	156/779 (20.0)	88/92 (95.7)
	Other VCT centre	30/779 (3.9)	0/92 (0.0)
Sociodemographic parameters			
Especially vulnerable groups	Transgender (FtM)	2/779 (0.3)	0/92 (0.0)
	Sold sex since last HIV test	29/779 (3.7)	0/92 (0.0)
	Previously diagnosed HIV	28/779 (3.6)	0/92 (0.0)
Age	<25 years	148/779 (19.0)	14/92 (15.2)
	25–39 years	393/779 (50.4)	55/92 (59.8)
	40+ years	238/779 (30.6)	23/92(25.0)
	Median (IQR)	33 (26; 42)	32 (27; 40)
Nationality	Swiss	543/779 (69.7)	85/92 (92.4)
	Neighbouring countries: AT, DE, FR, IT	116/779 (14.9)	2/92 (2.2)
	Latin American, ES, PT	53/779 (6.8)	0/92 (0.0)
	Other Western European, US, CA	21/779 (2.7)	0/92 (0.0)
	Eastern and South-eastern European	21/779 (2.7)	3/92 (3.3)
	African	10/779 (1.3)	1/92 (1.1)
	Asian	15/779 (1.9)	0/92 (0.0)
	Unknown	0/779 (0.0)	1/92 (1.1)
Legal status	Swiss	553/779 (69.7)	85/92 (92.4)
	Settlement permit	99/779 (12.7)	3/92 (3.3)
	Renewable/commuter permit	114/779 (14.6)	2/92 (2.2)
	Short-term permit or tourist	18/779 (2.3)	2/92 (2.2)
	No permit	5/779 (0.6)	0/92 (0.0)
Health insurance in Switzerland		734/764 (94.2)	89/91 (96.7)
Single / no steady partnership		356/751 (47.4)	33/92 (35.9)
Non-heterosexual identity*		757/779 (97.2)	0/92 (0.0)
Risk and precautionary behaviours			
Reports hepatitis B vaccination†		462/592 (78.0)	48/57 (84.2)
Reports HPV vaccination†		25/609 (4.1)	1/74 (1.4)
Previous history of diagnosed STIs‡		435/779 (44.2)	76/92 (17.4)
Number of sexual partners, previous 12 months	3–5	204/779 (26.2)	57/92 (62.0)
	6–10	240/779 (30.8)	25/92 (27.2)
	11–20	184/779 (23.6)	8/92 (8.7)
	21–50	112/779 (14.4)	2/92 (2.2)
	50+	39/779 (5.0)	0/92 (0.0)
Bought sex since last HIV test		51/779 (6.5)	22/92 (23.9)
Sex in a group, previous 12 months	No	464/779 (59.6)	83/92 (90.2)
	Yes, longer than 6 weeks ago	298/779 (38.3)	9/92 (9.8)
	Yes, in the last 6 weeks	17/779 (2.2)	0/92 (0.0)
Online acquisition of sex partners	None, previous 12 months	132/779 (16.9)	51/92 (55.4)
	Less than half, previous 12 months	129/779 (16.6)	26/92 (28.3)
	Half or more, previous 12 months	518/779 (66.5)	15/92 (16.3)
PrEP use§		8/779 (1.0)	0/92 (0.0)
CAVI, last 3 months		347/779 (44.5)	49/92 (46.7)
Negotiated safety	No steady partner	356/749 (47.5)	33/92 (35.9)
	No agreements	138/749 (18.4)	37/92 (40.2)
	Condom use outside partnership	255/749 (34.0)	22/92 (23.9)
IDU, previous 12 months		4/773 (0.5)	0/88 (0.0)
Sexualised drug use¶		235/743 (31.6)	14/89 (15.7)
Chemsex¶, previous 12 months		7/63 (11.1)	n.a.

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AT = Austria; CA = Canada; CAVI = condomless anal or vaginal intercourse; DE = Germany; ES = Spain; FR = France; FtM = female to male transition; HIV = human immunodeficiency virus; HPV = human papilloma virus; IDU = injection drug use; IQR = interquartile range; IT = Italy; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; PT = Portugal; STI = sexually transmitted infection; US = United States of America; VCT = voluntary counselling and testing. * Identifying as homosexual, bisexual, or other (but not as heterosexual) † Excluding participants who said they don't know. ‡ It was not specified what counted as an STI (other than HIV). § PrEP use was the only variable not self-reported but reported by medical staff. ¶ Sexualised drug use, consumption of poppers, cannabis, cocaine or synthetic drugs before or during sex; Chemsex, here defined as use of GHB/GBL, ketamine, crystal methamphetamine, or mephedrone "often or always when having sex" in the previous 12 months.

last HIV test. Among other multi-partner men, 16.3% had met at least half of their partners online and 23.9% had paid for sex since their last HIV test.

About half of male participants (44.5% vs 46.7%) reported condomless anal or vaginal intercourse in the past 3 months. Among respondents with a steady partner, MSM were more likely to report explicit agreements on condom use with non-steady partners ("negotiated safety": 64.9% vs 37.3%). Use of oral HIV chemoprophylaxis (PrEP) was not included in the clients' questionnaire but was documented for eight MSM (1.0%) at baseline.

Sexualised drug use was reported by 31.6% vs 15.7%. Injection drug use in the last 12 months was rare (0.5% of MSM), but 11.1% reported Chemsex "often or always when having sex". Although the baseline measure for Chemsex was based on only 63 participants, the follow-up measure was similar (9.8% of N = 582). Table 1 shows risk and precautionary behaviours.

Clinical outcomes: mental health, HIV/STIs, hepatitis B and C

In both groups one third of men showed signs of major depression in the PHQ-2 screening tool, and 11.9% of MSM vs 4.3% of other multi-partner men were sexually unhappy (p = 0.015).

Previously undiagnosed HIV was found in 0.5% vs 0.0% and *T. pallidum* antibodies in 15.3% vs 1.1% (p <0.001). For STIs requiring antibiotic treatment according to some guidelines at the time, we found active syphilis in 1.4% vs 0.0%, *N. gonorrhoeae* in 10.3% vs 0.0% (p <0.001), *C. trachomatis* in 8.7% vs 1.1% (p = 0.003), *T. vaginalis* in 3.2% vs 2.2% and *M. genitalium* in 5.3% vs 1.1% (p = 0.051). The collective measure for any of those five STIs was 25.6% vs 4.4%, corresponding to a number needed to screen (NNS) of 4 vs 23 (p <0.001).

When only bacterial infections with *N. gonorrhoeae*, *C. trachomatis*, and *T. pallidum* were considered to require treatment, the number needed to screen among MSM was still low (one in five), vs one in a hundred among other multi-partner men (p <0.001).

For viral hepatitis, 10.4% of MSM vs 1.3% of other multi-partner men had a history of hepatitis B (antibodies to hepatitis B core antigen [HBc-AB] positive, p = 0.003), 1.4% vs 1.3% had chronic hepatitis B (HBc-AB positive, antibodies to hepatitis B surface antigen [HBs-AB] negative) and 31.9% vs 47.3% had no immunity (HBs-AB <10 IU/l, p = 0.003). Among MSM, with use of this HBs-AB cut-off, the question relating to hepatitis B vaccination was 89.7% sensitive and 44.7% specific. Ten MSM had HCV antibodies (1.4%), with 8 out of the 10 being MSM with HIV; HCV seroprevalence was 0.6% among MSM without HIV infection known at baseline, and 0.3% among HIV-negative MSM. Three MSM (0.4%) had detectable HCV-RNA – all of them also had HIV. Table 2 shows the clinical outcomes.

Despite a rather small control group, the differences were statistically significant for a history of syphilis, current gonorrhoea, currant *C. trachomatis* infection, and for all combined outcomes. The differences were also statistically significant for a history of hepatitis B and lack of corresponding immunity.

Among MSM, with over 333.2 person years of follow-up, the proportion with incident STIs over 1 year of follow-up was slightly higher than prevalent STIs at baseline (fig. 1), but only the aggregated measure of "any of the five STIs" showed a significantly higher incidence. We found one incident HIV infection, corresponding to an incidence of 0.3%.

Multivariable models

In multivariable regression analysis (table 3) – further controlling for age, previous HIV status, transactional sex and group sex – inconsistent condom use (in the last 3 months) for anal/vaginal sex was not associated with STIs (neither was "negotiated safety", data not shown). Independent risk factors were sex with men (adjusted odds ratio [aOR] 16.4, 95% confidence interval [CI] 2.4–120.1) and the number of sexual partners (aOR 2.3 for >20, 95% CI 1.2–4.5).

When also controlled for reported symptoms, our findings were largely similar, but the variance explained by our model increased from 10% to 13%. Using alternative composite outcomes by adding *M. genitalium* and *T. vaginalis* did not substantially challenge these findings; however all effect size measures decreased and so did the explained variance.

Discussion

Among multi-partner MSM, but not among other multi-partner men, STIs, mostly asymptomatic, are common. In voluntary counselling and testing centres in Switzerland five multi-partner MSM need to be screened for bacterial STIs to find one with a notifiable and clinically relevant infection: syphilis, gonorrhoea, or chlamydia. One in four MSM acquired at least one of these bacterial STIs per year. Given that less than 4% of MSM had previously diagnosed HIV at baseline – less than half of what would have been expected [11] – our estimates may be conservative.

HIV

We found an HIV incidence of 0.3% per year in MSM, matching previous findings based on MSM population estimates and notification data [11, 12]. The baseline prevalence of previously *undiagnosed* HIV in MSM was similar (0.5%), suggesting HIV testing is frequent in this population.

Hepatitis B and C

This study confirms previous findings that HCV infections are concentrated in HIV-diagnosed MSM, but among MSM without diagnosed HIV do not exceed the prevalence in the general population. When results of the two

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published studies on HCV in non-HIV-diagnosed MSM in Switzerland (total n = 1454) are combined, HCV seroprevalence was 0.3% (95% CI 0.1–0.7) and HCV-RNA was present in 0.1% (95% CI 0.01–0.4) [9].This is not statistically different from our findings, with 0.3% (0.05–1.2) and 0.0% (0.0–0.4), respectively. It also suggests that between 2009 and 2016, HCV in non-HIV-diagnosed MSM in Switzerland has not increased.

In Switzerland, hepatitis B vaccination is recommended and reimbursed for all adolescents as well as men and women with "frequently changing partners" [13]. All study participants were eligible for hepatitis B vaccination. Although previous hepatitis B infection correlated positively with age, MSM had an overall prevalence of 10% of HBc-AB, much higher than among other multi-partner men, which suggests the promotion of hepatitis B vaccination among MSM should be prioritised. A third of MSM showed evidence of no or insufficient vaccination, despite a conservative cut-off of <10 IU/l. Whereas the question on self-reported hepatitis B vaccination showed a high sensitivity for detecting individuals with previous vaccination, it was not very specific and thus overestimates true vaccination status. This has implications for monitoring vaccination coverage.

Non-viral STIs

Fifteen per cent of MSM showed evidence of prior syphilis infection, matching the 15.4% reported in one of the largest studies of MSM living in Switzerland (EMIS-2017) [14] After a historic nadir around the year 2000, syphilis incidence has steadily increased [15]. Epidemiological models have suggested that even sustainable interventions around partner reduction or increasing condom use would have limited effects [16], and the US Centers for Disease Control's syphilis elimination plan officially ended in 2013 [17]. Among MSM in this study, the baseline prevalence of active syphilis was 1.7%, and the incidence was 4.2 per

Table 2: Clinical outcomes. Mental health, HIV, STIs, Hepatitis B and C, percentages with 95% confidence intervals.

Prevalence at baseline		**MSM % (95% CI)**	**Other men % (95% CI)**
Persons with baseline visit		n = 779	n = 92
Mental Health	Sexually unhappy	11.9 (9.8–14.5)	4.3 (1.4–11.4)
	Signs of major depression (PHQ-2 variant)	31.8 (28.6–35.3)	31.5 (22.5–42.2)
HIV	Newly diagnosed HIV	0.5 (0.2–1.4)	0.0 (0.0–3.3)
STIs	Active syphilis (treatment)	1.7 (0.9–2.9)	0.0 (0.0–3.3)
	T. pallidum IgG/M positive	15.3 (12.9–18.0)	1.1 (0.1–6.8)
	High RPR/VDRL (reactive at 1: ≥8)	1.3 (0.7–1.4)	0.0 (0.0–3.3)
	N. gonorrhoeae	10.3 (8.3–12.7)	0.0 (0.0–3.3)
	C. trachomatis	8.7 (6.9–11.0)	1.1 (0.1–6.8)
	T. vaginalis	3.2 (2.1–4.8)	2.2 (0.4–8.4)
	M. genitalium	5.3 (3.8–7.1)	1.1 (0.1–6.8)
	Active syphilis, NG, or CT	19.0 (16.3–22.0)	1.1 (0.1–6.8)
	Active syphilis, NG, CT, or TV	21.4 (18.6–24.5)	3.3 (0.8–9.9)
	Active syphilis, NG, CT, TV, or MG	25.5 (22.5–28.8)	4.3 (1.4–11.4)
	Reporting STI symptoms*	15.0 (12.6–17.7)	12.0 (6.4–20.8)
Hepatitis B and C	No. persons with HBs-AB (HBc-AB, HCV-AB)	n = 775 (511, 724)	n = 91 (77, n.a.)
	HBs-AB <10 IU/l	31.9 (28.6–35.3)	47.3 (36.8–57.9)
	HBc-AB positive	10.4 (8.0–13.5)	1.3 (1.2–6.7)
	HBc-AB positive, HBs-AB negative	1.4 (0.6–3.0)	1.3 (0.1–8.1)
	HCV-AB	1.4 (0.8–2.7)	n.a.
	HCV-RNA	0.4 (0.1–1.3)	n.a.
	HCV-AB among HIV-negative	0.3 (0.05–1.2)	n.a.
	HCV-RNA among HIV-negative	0.0 (0.0–0.4)	n.a.
Yearly incidence during follow-up		MSM % (95% CI)	
Persons with follow-up visits		n = 526	
Follow up visits		n = 623	
Person-years of follow up		333.2 years	
HIV	Newly diagnosed HIV	0.3 (0.04–2.2)	
STIs	Active syphilis (treatment)	4.2 (2.5–7.0)	
	High RPR/VDRL (reactive at 1: ≥8)	2.1 (1.0–4.4	
	N. gonorrhoeae	14.7 (11.4–19.0)	
	C. trachomatis	9.0 (6.4–12.7)	
	T. vaginalis	5.4 (3.4–8.5)	
	M. genitalium	6.3 (4.2–9.5)	
	Active syphilis, NG, or CT	25.5 (21.2–30.6)	
	Active syphilis, NG, CT, or TV	30.6 (26.0–36.0)	
	Active syphilis, NG, CT, TV, or MG	36.9 (32.1–42.5)	

AB = antibodies; CI = confidence interval; CT = *C. trachomatis*; MSM = men who have sex with men; HBc = hepatitis B core; HBs = hepatitis B surface; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgG/M = immunoglobulin G/M; IU = international units; MG = *M. genitalium*; MSM = men who have sex with men; NG = *N. gonorrhoeae*; PHQ = patient health questionnaire; RPR = rapid plasma reagin; STI = sexually transmitted infection; TV = *T. vaginalis*; VDRL = venereal diseases research laboratory. * Participants were shown a comprehensive list of STI symptoms and asked if they currently had any of them.

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100 person-years. This compares to 74 per 100 person-years among HIV-positive MSM in the Swiss HIV Cohort Study in 2014 [18], corroborating previous findings that the current syphilis epidemic is concentrated in sexual networks of MSM in general, and in sexual networks of HIV-positive MSM in particular. Given that syphilis incidence

Figure 1: Sexually transmitted infections among men who have sex with men at baseline (n = 779) and during follow-up (n = 526 over 623 follow-up visits; 333.2 years of follow-up); percent with 95% confidence intervals. CT = *C. trachomatis*; MG = *M. genitalium*; NG = *N. gonorrhoeae*; TV = *T. vaginalis*.

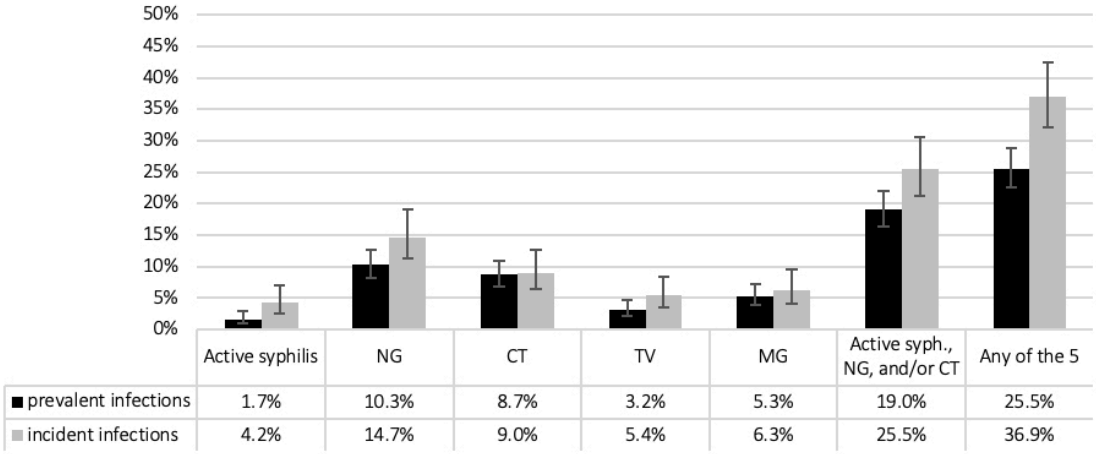

Table 3: Uni- and multivariable regression models.

Regression model		Univariable OR (95% CI)	Multivariable 1 AOR (95% CI)	Multivariable 2 AOR (95% CI
Persons with baseline visit		**N = 871**	**N = 871**	**N = 871**
Nagelkerke's R^2		–	9.8% *7.8%*	12.5% *9.0%*
Age	40+ years	1	1	1
	25–39 years	1.38 (0.90–2.11) *1.20 (0.83–1.74)*	1.47 (0.94–2.28) *1.27 (0.86–1.86)*	1.42 (0.91–2.22) *1.24 (0.84–1.82)*
	<25 years	1.54 (0.91–2.96) *1.34 (0.85–2.13)*	1.62 (0.93–2.84) *1.43 (0.87–2.33)*	1.51 (0.86–2.66) *1.37 (0.84–2.24)*
Previous HIV diagnosis	No	1	1	1
	Yes	1.65 (0.69–3.94) ***2.19*** *(1.01–4.76)*	1.20 (0.48–2.96) *1.74 (0.78–3.88)*	1.13 (0.45–2.86) *1.70 (0.76–3.83)*
Sold sex since last HIV test	No	1	1	1
	Yes	**2.66** (1.21–5.85) *2.07 (0.96–4.46)*	1.81 (0.80–4.06) *1.47 (0.67–3.23)*	1.63 (0.71–3.75) *1.37 (0.62–3.05)*
Bought sex since last HIV test	No	1	1	1
	Yes	0.66 (0.32–1.36) *0.56 (0.29–1.09)*	1.03 (0.48–2.21) *0.79 (0.39–1.59)*	0.99 (0.46–2.15) *0.77 (0.38–1.56)*
Number of sexual partners, previous 12 months	3–5	1	1	1
	6–10	**1.86** (1.09–3.17) ***1.74*** *(1.12–2.71)*	1.56 (0.88–2.73) *1.43 (0.89–2.32)*	**1.81** (1.01–3.23) *1.56 (0.96–2.53)*
	11–20	**2.94** (1.71–5.03) ***2.11*** *(1.33–3.37)*	**2.22** (1.20–4.10) *1.53 (0.89–2.63)*	**2.42** (1.29–4.53) *1.59 (0.92–2.75)*
	20+	**3.38** (1.94–5.89) ***2.76*** *(1.71–4.46)*	**2.31** (1.19–4.48) ***1.84*** *(1.03–3.30)*	**2.45** (1.25–4.78) ***1.89*** *(1.05–3.39)*
Sex in a group, previous 12 months	No	1	1	1
	Yes	**1.71** (1.20–2.44) ***1.68*** *(1.22–2.30)*	1.03 (0.66–1.59) *1.15 (0.77–1.72)*	1.06 (0.68–1.65) *1.18 (0.79–1.76)*
CAVI, previous 3 months	No	1	1	1
	Yes	**1.49** (1.05–2.13) *1.30 (0.95–1.78)*	1.33 (0.91–1.93) *1.15 (0.82–1.60)*	1.25 (0.86–1.83) *1.10 (0.79–1.55)*
Sex with men in the past 12 months	No	1	1	1
	Yes	**21.34** (2.95–154.41) ***7.55*** *(2.74–20.83)*	**16.40** (2.38–120.12) ***5.77*** *(2.06–16.21)*	**16.06** (2.19–117.94) ***5.65*** *(2.01–15.87)*
Reporting STI symptoms	No	1	–	1
	Yes	**2.52** (1.65–3.87) ***1.84*** *(1.23–2.77)*	–	**2.53** (1.60–3.99) ***1.84*** *(1.20–2.83)*

(A)OR = (adjusted) Odds Ratio; CAVI = condomless anal or vaginal intercourse; CI = confidence interval; CT = *C. trachomatis*; MG = *M. genitalium*; NG = *N. gonorrhoeae*; STI = sexually transmitted infection; TV = *T. vaginalis*Data presented are crude and adjusted odds ratios (**bold** if p <0.05) with 95% confidence intervals. Combined endpoints: diagnosis of active syphilis, NG, or CT; and – *in italics* – diagnosis of active syphilis, NG, CT, TV, or MG among men.

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in this study was 10 times higher than HIV incidence, we agree with Australian guidelines that testing MSM for syphilis only once per year may not be sufficient to control the epidemic [19].

As urethral infections with *N. gonorrhoeae* are typically symptomatic and lead to medical consultation [20], most cases of gonorrhoea in this study are likely to have been present in the rectum, and/or in the oropharynx. The majority of *N. gonorrhoeae* / *C. trachomatis* infections in MSM are missed if asymptomatic testing is restricted to a urine specimen [21]. Pharyngeal screening is not implemented in many national guidelines, but the contribution of fellatio to transmission of not only *N. gonorrhoeae* but also *C. trachomatis* has been demonstrated [4]. This means all *N. gonorrhoeae* / *C. trachomatis* detected in this study would likely contribute to onward transmission if left untreated, as self-clearance of asymptomatic infections takes longer (>100 days) [22] than the time to the next sexual encounter – at least on average in MSM with three or more partners per year.

It has been proposed that *C. trachomatis* infection control programmes based on early detection and treatment might interfere with the effects of immunity on population susceptibility to infection. The same authors suggest two strategies to decrease *C. trachomatis* infections at the population level: developing a vaccine or strategies to alter sexual networks [23]. Whereas in settings with low *C. trachomatis* prevalence (e.g., <5% in young adults), opportunistic testing may not result in "sizeable reductions" in chlamydia prevalence [24]; *C. trachomatis* prevalence was higher in this and other studies [25] of MSM, and asymptomatic rectal chlamydial infections in MSM have been proposed as an important reservoir fuelling transmission [26]. As 90% (unpublished data FOPH) of *N. gonorrhoeae* / *C. trachomatis* diagnoses in Switzerland are based on nucleic acid amplification technique (NAAT), it would also be difficult to screen for gonorrhoea alone.

Infections with *T. vaginalis* among MSM were not uncommon, although less frequent than *N. gonorrhoeae* / *C. trachomatis* and not significantly higher than in other multi-partner men. Other research has suggested that *T. vaginalis* may circulate within MSM networks and not result from concurrent sexual contact with women [27]. Our multivariable model suggests that transmission of *T. vaginalis* (and *M. genitalium*) is less specific to MSM, and less dependent on typical STI determinants such as the number of sexual partners. Given the substantial side-effects of metronidazole (standard treatment for *T. vaginalis*), the high rates of antimicrobial resistance of *M. genitalium*, and the unclear public health impact of infections with *T. vaginalis* / *M. genitalium*, we do not recommend routine testing of men for *T. vaginalis* or *M. genitalium*. *M. genitalium* will be analysed in a subsequent paper.

Risk and precautionary behaviour

Slightly more than half of men reported consistent condom use for anal or vaginal sex, with no significant difference between the two groups. In Switzerland at the time of enrolment, PrEP was recommended for men and women at high risk for HIV [28], but not implemented and only available through online importation. Two years later, 4% of HIV-negative MSM reported current PrEP use [29], two thirds of them accessing PrEP informally online [14].

MSM reported much higher numbers of sexual partners than other multi-partner men. The distribution of partner numbers in the last 12 months almost perfectly reflected EMIS-2017 results, when the Swiss EMIS-2017 data was restricted to the sub-sample to men with 3+ partners (two thirds of the total): 3–10 partners, 62% (STAR) vs 56% (EMIS-2017); 11–20 partners, 19% vs 23%; 21–50 partners, 14% vs 14%, 50+ partners, 6% vs 7% [14]. Contrastingly, the majority of heterosexual men in STAR had only 3 to 5 sexual partners in the previous 12 months, but they were much more likely to report having paid for sex when compared with MSM.

Group sex and sexualised drug use were common among MSM. The proportion of MSM engaging in Chemsex was similar to other recently published studies from Switzerland – for example, the 11.8% of EMIS-2017 respondents in Switzerland reporting stimulant drugs in the last 12 months [14], or the 7.9% based on the same online tool but with a much larger sample size [30]. The difference from the latter publication might be attributable to our restriction to multi-partner men. What these studies have in common is the anonymous nature of reporting illicit/stigmatised behaviour. Surprisingly, Chemsex figures were not higher among HIV-positive MSM in the Swiss HIV Cohort Study [31], possibly indicating under-reporting of illicit/stigmatised behaviour in a clinical interview setting.

Since 2016, HPV vaccination has been recommended and reimbursed also for boys and men younger than 27 [32]. A result of 7% to 8% self-reported coverage among men in the eligible age group is an excellent outcome for the first year of implementation for men.

Strengths and limitations

The strengths of this study include the large sample size of MSM, the high rate of follow-up, and the rigorous methodology with respect to comprehensive STI testing. The study was sufficiently powered to detect even rare infections such as hepatitis C. The study participants represented a broad range of men with respect to age, nationality, legal status and place of residence. Although the country's Italian-speaking part was clearly under-represented, we think that our MSM results are largely representative for sexually active gay and bisexual men in Switzerland.

This study has several limitations. It was not sufficiently powered to calculate the incidence of STIs among multi-partner men who exclusively have sex with women. The pooling of meatal/urethral, anal and pharyngeal swabs precludes the possibility of calculating site-specific prevalences, and also might lead to an underestimation of pharyngeal and thus overall *N. gonorrhoeae* infections [33]. Another major limitation is the absence of any test of cure. However, we think it is unlikely that syphilis, *N. gonorrhoeae* or *C. trachomatis* were not cured by standard treatment. Persisting infections would lead to an overestimation of incident cases, which is one of the reasons for not including MG or TV in our main outcome variable for incident STIs.

It needs to be highlighted that all behavioural data were self-reported. The finding that condom use was not protective against STIs (fig. S2 in appendix 1) has to be inter-

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preted with caution. However, oral sex in MSM is typically condom-free – both fellatio [34] and oro-anal sex [35]. Although condoms effectively prevent contact with ejaculate, their effect of reducing mucosal contact over the whole course of sexual encounters is limited. In the common scenario of anal fingering prior to intercourse, transmission of STIs is possible via smear infection before or at the time of condom application.

Implications

The high incidence-to-prevalence ratio of the combined endpoint (active syphilis, gonorrhoea, or chlamydia) suggests that annual screening may be insufficient to control the epidemic of these three STIs in MSM. Biannual screening might be more adequate as a standard for multi-partner MSM [36], particularly for those with more than 10 partners per year. Other research has also suggested specifying situations in which culture-based testing is needed to provide information about anti-microbial resistance in *N. gonorrhoeae* [20]. Given the high prevalence and incidence of gonorrhoea among multi-partner MSM, this population is a good target for additional culture testing, with costs borne by the health care system rather than by the client. The best testing frequency MSM still needs to be determined by mathematical modelling, and in Switzerland the online counselling tool used in voluntary counselling and testing centres could include an algorithm to estimate the best individual interval for repeat testing based on personal data. Routine testing of heterosexual multi-partner men is not supported by our findings. Being part of a dense sexual network with a high turn-over of sexual partners may have a much larger impact on STI transmission than individual sexual behaviour [37, 38].

Conclusions

This study supports previous recommendations for MSM that syphilis testing and nucleic acid amplification technology-based screening for *N. gonorrhoea* (combined with *C. trachomatis*) at extra-genital sites [25] should be widely available, and providers should be educated about appropriate screening practice [19, 39, 40]. However, recommending regular testing in asymptomatic multi-partner individuals for the benefit of public health is pointless if it is not affordable to those at risk. MSM at highest risk of infection would have to spend more than US$ 2000 PPP [8] per year if screened for example every 3 months. The current price system in Switzerland may lead to substantial undertesting [20] and thus impede STI control among MSM. Given the high risk of onward transmission of bacterial STIs, low-cost or free routine screening of multi-partner MSM is a public health priority.

Preliminary data of this study were presented at the 31st annual IUSTI Europe conference in Helsinki, Finland (IUSTI17-47, IUSTI17-53) in August/September 2017, and at the Swiss HIV&STI Forum in March 2018.

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Author contributions

AJS coordinated and conceptualised the study, participated in data acquisition and supervised the study in St. Gallen, cleaned the data, performed the statistical analyses and wrote the manuscript. AL participated in the study design and helped with the organisation of outreach work. CE participated in data acquisition, supervised the study at PROFA, Canton of Vaud, and proof-read the manuscript. CVH participated in data acquisition and supervised the study at Inselspital, Bern. FJ participated in data acquisition at Checkpoint Vaud. KL participated in data acquisition at Checkpoint Basel. MRa coordinated the ethics approval, the laboratory collaboration, participated in data acquisition, supervised overall data entry, and organised MSM outreach work in Eastern Switzerland and Zurich. MRi supervised all PCR lab work and evaluated the raw data. MS participated in data acquisition and supervised the study at Checkpoint Basel. TK participated in data acquisition at Inselspital, Bern. TL supervised all serology laboratory work and evaluated the raw data. PV organised the funding, initiated and conceptualised the study, participated in data acquisition and cleaning of laboratory data, and substantially contributed to the manuscript. VC participated in data acquisition and supervised the study at Checkpoint Vaud. All authors contributed to the manuscript and approved the final version.

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Potential competing interests

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Appendix 1: Methods in detail

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