RESEARCH ARTICLE

Assessing the drivers of syphilis among men who have sex with men in Switzerland reveals a key impact of screening frequency: A modelling study

Suraj Balakrishna[1,2☯*], Luisa Salazar-Vizcaya[3☯], Axel J. Schmidt[4,5], Viacheslav Kachalov[1,2], Katharina Kusejko[1,2], Maria Christine Thurnheer[3], Jan A. Roth[6,7,8], Dunja Nicca[9], Matthias Cavassini[10], Manuel Battegay[6], Patrick Schmid[4], Enos Bernasconi[11], Huldrych F. Günthard[1,2], Andri Rauch[3‡], Roger D. Kouyos[1,2‡], the Swiss HIV Cohort Study (SHCS)[¶]

1 Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland, 2 Institute of Medical Virology, University of Zurich, Zurich, Switzerland, 3 Department of Infectious Diseases, Bern University Hospital, University of Bern, Bern, Switzerland, 4 Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St. Gallen, Switzerland, 5 Sigma Research, London School of Hygiene and Tropical Medicine, United Kingdom, 6 Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, University of Basel, Basel, Switzerland, 7 Basel Institute for Clinical Epidemiology, University Hospital Basel, Basel, Switzerland, 8 Division of Research and Analytical Services, Department of Informatics, University Hospital Basel, Basel, Switzerland, 9 Institute of Nursing Science, University of Basel, Basel, Switzerland, 10 Division of Infectious Diseases, Lausanne University Hospital, Lausanne, Switzerland, 11 Division of Infectious Diseases, Regional Hospital Lugano, Lugano, Switzerland

☯ These authors contributed equally to this work.
‡ AR and RDK also contributed equally to this work.
¶ Membership of the Swiss HIV Cohort Study (SHCS) is listed in the Acknowledgments.
* suraj.balakrishna@usz.ch

Abstract

Over the last decade, syphilis diagnoses among men-who-have-sex-with-men (MSM) have strongly increased in Europe. Understanding the drivers of the ongoing epidemic may aid to curb transmissions. In order to identify the drivers of syphilis transmission in MSM in Switzerland between 2006 and 2017 as well as the effect of potential interventions, we set up an epidemiological model stratified by syphilis stage, HIV-diagnosis, and behavioral factors to account for syphilis infectiousness and risk for transmission. In the main model, we used 'reported non-steady partners' (nsP) as the main proxy for sexual risk. We parameterized the model using data from the Swiss HIV Cohort Study, Swiss Voluntary Counselling and Testing center, cross-sectional surveys among the Swiss MSM population, and published syphilis notifications from the Federal Office of Public Health. The main model reproduced the increase in syphilis diagnoses from 168 cases in 2006 to 418 cases in 2017. It estimated that between 2006 and 2017, MSM with HIV diagnosis had 45.9 times the median syphilis incidence of MSM without HIV diagnosis. Defining risk as condomless anal intercourse with nsP decreased model accuracy (sum of squared weighted residuals, 378.8 vs. 148.3). Counterfactual scenarios suggested that increasing screening of MSM without HIV diagnosis and with nsP from once every two years to twice per year may reduce syphilis incidence (at most 12.8% reduction by 2017). Whereas, increasing screening among MSM with HIV

diagnosis and with nsP from once per year to twice per year may substantially reduce syphilis incidence over time (at least 63.5% reduction by 2017). The model suggests that reporting nsP regardless of condom use is suitable for risk stratification when modelling syphilis transmission. More frequent screening of MSM with HIV diagnosis, particularly those with nsP may aid to curb syphilis transmission.

Author summary

Syphilis, one of the most common sexually transmitted infections, remains a major public health problem. Over the last decade, a rising number of diagnoses especially in men-who-have-sex-with-men (MSM) was observed in Western Europe and Northern America. In Switzerland, the number of syphilis diagnoses in MSM tripled between 2006 and 2017. In this study, we used a mathematical model to assess the drivers of this increase among MSM in Switzerland. Our model could reproduce the increase in syphilis diagnoses in both MSM with and without HIV diagnosis between 2006 and 2017. Based on this model we found that MSM with HIV diagnosis have an over 45 times higher syphilis incidence than MSM without HIV diagnosis. Furthermore, we found that reported sex with non-steady partners is a useful proxy of behavioral risk. Considering counterfactual scenarios, we showed that increasing the screening frequency for syphilis among MSM with HIV diagnosis and with non-steady partners from once a year to twice per year can reduce syphilis incidence by 63.5% to 99.2%.

Introduction

Syphilis, a sexually transmitted infection caused by bacteria *Treponema pallidum*, remains a major public health problem. Over the last decade, a rising number of diagnoses especially in men-who-have-sex-with-men (MSM) was observed in Western Europe and Northern America [1–3]. In Switzerland, the number of syphilis diagnoses in MSM tripled between 2006 and 2017 [4]. A similar trend was observed for the incidence rate of syphilis in HIV-diagnosed MSM in the Swiss HIV Cohort Study (SHCS) [5–7]. Syphilis and HIV co-infections are common, and syphilis has been associated with an increased risk or HIV transmission [8]. Understanding syphilis transmission dynamics while considering the role of HIV infection could provide insights towards more effective prevention efforts to reduce the incidence of syphilis.

The syphilis incidence in a population is largely determined by parameters such as the transmission probability per sexual partnership, the average rate of acquisition of sexual partners and the duration of infectiousness, as well as by the prevalence of practices such as–oral sex, condomless anal intercourse, multiple sexual partnership, and anal intercourse with non-steady partners [9,10]. Prevention strategies, such as the promotion of condom use, risk-reduction counselling, and syphilis screening and treatment, have the potential to alter syphilis rates by modifying these key parameters [11]. Recent studies show a decrease in condom use for anal sex in MSM with HIV diagnosis [11,12]. This situation may have caused the increased incidence of syphilis.

The natural course of syphilis has four stages: primary, secondary, latent, and tertiary. Almost all syphilis transmissions occur through direct skin-to-skin contact with active lesions during the primary and secondary stages and the disease remains transmissible for an average period of two to three months [13]. Studies have estimated the attack rate of syphilis within 30 days of exposure to sexual transmission of syphilis to be between 16 and 30% [14,15]. During

the latent stage of syphilis, there are no clinical signs or symptoms of syphilis. If left untreated, the infection may reach its tertiary stage and may affect different organ systems. Hence it is essential to diagnose and treat people infected with syphilis as early as possible. A stepped wedge cluster randomized controlled trial showed that the routinized syphilis screening among men living with HIV increased the syphilis diagnosis [16]. Previous modelling studies suggest that more frequent syphilis screening could reduce incidence [17–20].

We aimed to identify possible drivers of the ongoing syphilis epidemic among MSM in Switzerland using a mathematical model (Fig 1) and to characterize the role of behavioral predictors (proxies for transmission risk of syphilis) that could best explain the changes in syphilis incidence observed over the last decade. Based on this model, we evaluated the effect of different screening strategies on syphilis incidence.

Methods

Ethics statement

The SHCS was approved by the local ethical committees of the participating centers: Kantonale Ethikkommission Zürich (KEK-ZH-NR: EK-793); Ethikkommission beider Basel ("Die Ethikkommission beider Basel hat die Dokumente zur Studie zustimmend zur Kenntnis genommen und genehmigt."); Kantonale Ethikkommission Bern (21/88); Comité départemental d'éthique des spécialités médicales es de médecine communautaire et de premier recours, Hôpitaux Universitaires de Genève (01–142); Commission cantonale d'éthique de la recherche sur l'être humain, Canton de Vaud (131/01); Comitato etico cantonale, Repubblica e Cantone Ticino (CE 813); Ethikkommission des Kantons St. Gallen (EKSG 12/003), and written informed consent was obtained from all participants.

We used data from the SHCS and cross-sectional surveys among the Swiss MSM population to estimate the transmission risk of syphilis. These temporal trends were used to parameterize a mathematical model, which was then used to assess the impact of different screening strategies via counterfactual scenarios (see Fig 1 for an overview of the workflow).

Data

Our model population comprised all MSM in Switzerland from 2006 to 2018. We estimated the number of MSM in Switzerland between 2006 and 2018 based on the demographic dynamics of Switzerland by the Federal Statistical Office, Switzerland and Schmidt and Altpeter, 2019 [21,22]. In Switzerland, all syphilis cases are anonymously reported to the Federal Office of Public Health (FOPH) [4].

Approximately 80% of all HIV-diagnosed MSM in Switzerland are enrolled in the Swiss HIV Cohort Study (SHCS) [22,23]. The SHCS is a prospective multicenter cohort study, which systematically collects epidemiological and clinical data for more than 20000 HIV-diagnosed persons of age 16 or older in Switzerland since 1988 [24]. After the restart of routine syphilis screening in the SHCS in 2004, MSM are being tested for syphilis annually with treponemal and non-treponemal tests. We defined the first syphilis episode as a positive treponemal test after a negative treponemal test result. A $\geq$4-fold titer reduction or negativity in non-treponemal test result after an episode of syphilis indicate the absence of active syphilis. We defined subsequent episode(s) of syphilis as a subsequent $\geq$4-fold titer increase with a titer value of at least eight in non-treponemal test.

Patterns of transmission risk

We estimated the proportion of MSM with HIV diagnosis (MSM_{wHD}) and with non-steady partners (nsP) based on the SHCS data. We estimated the yearly rates of switching from
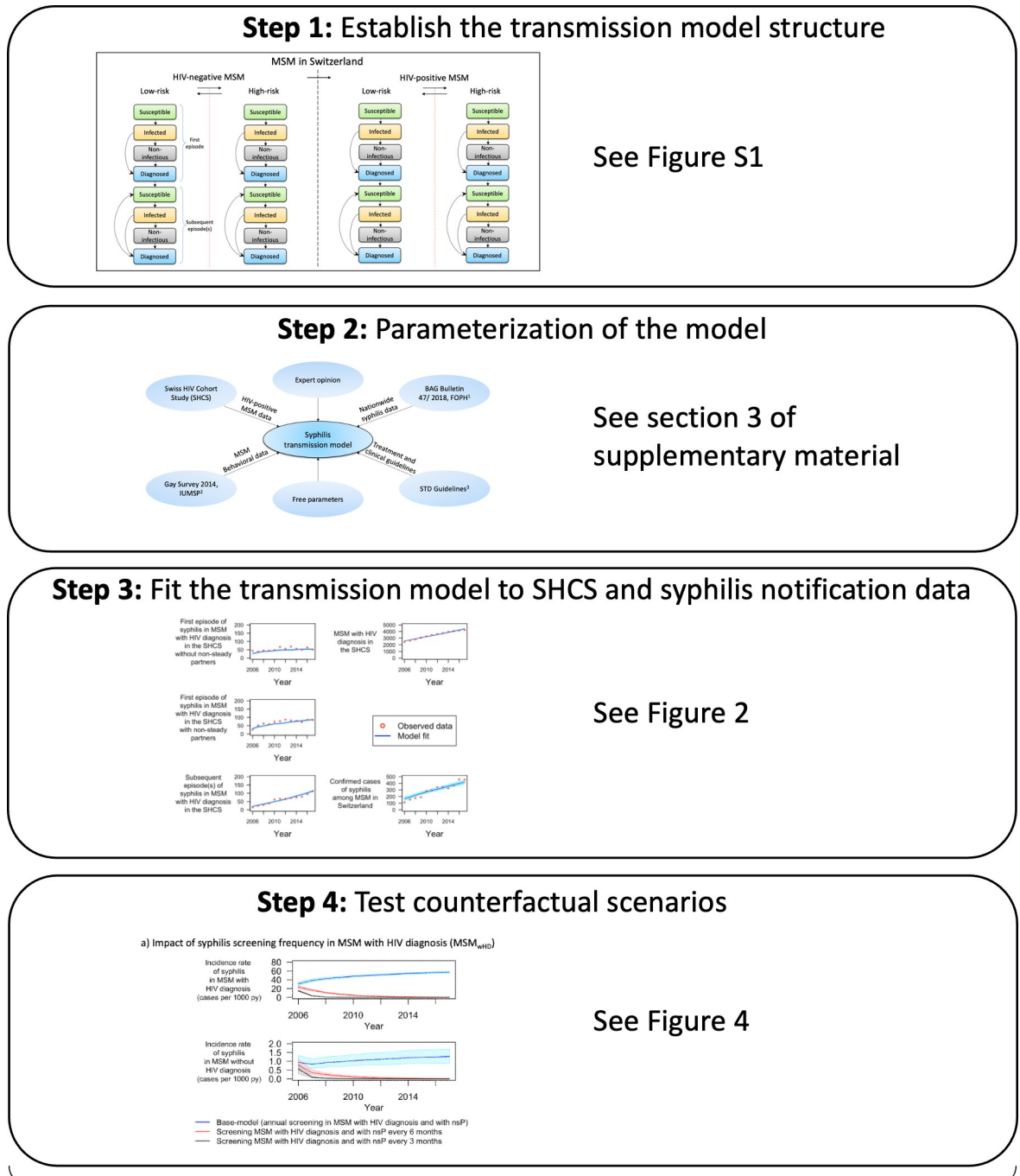
Fig 1. Schematic overview of the methods.

MSM_{wHD} with nsP to MSM_{wHD} without nsP and vice-versa using time-to-event survival analysis (section 6 in S1 Text). In contrast, we estimated an analogous proportion for MSM without HIV diagnosis ($MSM_{w/oHD}$) from published survey data (*Gaysurvey*) [25]. *Gaysurvey* was a series of anonymous internet-based self-administered surveys periodically conducted in

Switzerland among MSM since 1987. It was a part of the monitoring system established by the FOPH as a tool for monitoring risk behavior among MSM in Switzerland. In the last *Gaysurvey* in 2014, 834 people participated in the *Gaysurvey* and had a median age of 40 years. About 97% of these participants identified themselves either as gay/homosexual (84.1%) or bisexual (12.8%). As the data is not longitudinal at the individual level and is available for only a couple of years, a linear interpolation and a constant extrapolation was used to estimate the proportion of MSM with non-steady partners for $MSM_{w/oHD}$. As the participants of *Gaysurvey* were not followed up over time and hence participants could be different at each time point of survey conduction, we assumed a constant rate of switching back to $MSM_{w/oHD}$ with nsP from $MSM_{w/oHD}$ without nsP. We fixed this rate to the mean rate of switching back to MSM_{wHD} with nsP from MSM_{wHD} without nsP for the years 2006 and 2017. Based on this assumption, we estimated that the yearly rates of switching from $MSM_{w/oHD}$ without nsP to $MSM_{w/oHD}$ with nsP using a spline function (section 6 in S1 Text).

Model of syphilis transmission

To model the syphilis epidemic in MSM in Switzerland between 2006 and 2017, we set up a system of 32 coupled ordinary differential equations (See section 2 in S1 Text for the model equations). We stratified the mathematical model by syphilis stage and cascade of care to account for infectiousness and disease progression into four levels: susceptible (MSM who do not have syphilis and can become infected with syphilis), infected (MSM who are infected with syphilis and can transmit; infectious), latent (MSM who are infected with syphilis but cannot transmit; non-infectious) and diagnosed (MSM diagnosed with syphilis) (Fig A in S1 Text). We did not include a 'treated' compartment as diagnosed individuals are assumed to be immediately treated and to clear from the infection within one month [13]. We further stratified the model by reported non-steady partners to account for increased transmission risk of syphilis. Additional layers in the model include HIV status ($MSM_{w/oHD}$ vs. MSM_{wHD}), the episode of syphilis: first (MSM who never had syphilis before) or subsequent (MSM who had at least one episode of syphilis before). Susceptible MSM become infected with syphilis with a force of infection (Λ) due to sexual contact with MSM infected with syphilis (section 3.3 in S1 Text). Infected MSM are infectious during the primary and secondary stages of syphilis that together last about 2–3 months after transmission. After this period, infected MSM enter the latent stage of syphilis during which the infection will no longer contribute to Λ. We further assume that infected and latently infected MSM would be diagnosed with syphilis if they are tested for syphilis and that all diagnosed MSM are immediately treated. Treated men would clear syphilis and become susceptible for subsequent episodes of syphilis. A complete description of the model, including model equations, is available in sections 1 and 2 in S1 Text.

Changes in transmission risk such as MSM with non-steady partners (nsP), as well as syphilis diagnosis and treatment rates among the MSM_{wHD} were derived from the SHCS data, while changes in sexual risk behaviour among $MSM_{w/oHD}$ were derived from the *Gaysurvey*. Diagnosis rate and treatment rate of syphilis among the $MSM_{w/oHD}$ were derived from the literature, and Voluntary Counselling and Testing (VCT) data (Table B in S1 Text).

Parameters governing the transmission of syphilis and the syphilis incidence rate among the MSM_{wHD} not enrolled in the SHCS were assumed to be the same as the MSM_{wHD} enrolled in the SHCS. Parameters that could not be obtained from databases and literature such as transmission rate of syphilis, transmission rate of HIV, risk-sorting behaviour, and initial number of MSM infected with syphilis in 2006 were derived by fitting the model to data on syphilis cases among the MSM_{wHD} and $MSM_{w/oHD}$ in Switzerland. This fit was done by minimizing the sum of squared weighted residuals between each observed and predicted datapoint

assuming normally distributed errors (section 7 in S1 Text). We further used simplified Markov chain Monte Carlo (MCMC), based on an adaptive Metropolis algorithm and including a delayed rejection procedure, with prior values specified by the distribution of the parameters to obtain their posterior distributions using the package "A Flexible Modelling Environment for Inverse Modelling, Sensitivity, Identifiability, and Monte Carlo Analysis (FME)" in R version 4.0.0 [26,27]. We used independent and uniform priors within *ad hoc* bounds for the free parameters (Table A in S1 Text). In a sensitivity analysis, we also fitted the model through maximization of the likelihood by assuming Poisson distributed incident cases of syphilis and compared the model fits.

Counterfactual scenarios

We compared the incidence of syphilis obtained with the main model fit with that simulated when assuming the following two alternative scenarios. Firstly, we considered the impact of change in transmission risk (reported nsP in MSM) between the years 2006 and 2018 by assuming after 2006 no change in the proportion of MSM switching from with nsP to without nsP and vice-versa. Secondly, we considered the impact of change in screening frequency for syphilis between the years 2006 and 2018. We estimated the influence of this frequency by assuming an increase (by a given factor) of the screening frequency among MSM_{wHD} and $MSM_{w/oHD}$ with non-steady partners.

Sensitivity analysis

To test the robustness of the model and possible inconsistencies in data, we recalibrated the model in the following six ways: firstly, we used "reported condomless anal intercourse with non-steady partners" (nsCAI) as the proxy for sexual risk instead of nsP. Secondly, we assessed the impact of assuming the same transmission rate for MSM_{wHD} and $MSM_{w/oHD}$ but taking into account a potential underreporting of syphilis cases among MSM without HIV diagnosis. Thirdly, we investigated the impact of a possible overestimation of transmission risk among MSM without HIV diagnosis. Fourthly, we assessed the impact of potential infectiousness of syphilis in the latent stage on the dependency between screening frequency and syphilis incidence. Fifthly, we tested the effect of model fitting through maximization of the likelihood by assuming Poisson distributed incident cases of syphilis. Finally, we tested the robustness of our model results to fixed parameter sets by sampling 50 sets of fixed parameters from given bounds around the point estimates using a Latin hypercube sampling algorithm. Sampling was followed by model optimization, and counterfactual scenario analyses.

Results

Data

Our mathematical model simulates transmission dynamics of syphilis in the MSM population in Switzerland from 2006 to 2018. Based on the Federal Statistical Office, Switzerland and Schmidt and Altpeter, 2019, we estimated the number of MSM in Switzerland in 2006 and 2018 to be 75016 and 85325, respectively (Fig B in S1 Text) [21,22]. There were 113 and 456 cases of syphilis reported to the FOPH in 2006 and 2018, respectively [4].

To estimate the number of MSM with HIV diagnosis (MSM_{wHD}) in Switzerland from 2006 and 2018 and the syphilis cases among them, we analyzed 5382 MSM enrolled in the Swiss HIV cohort study (SHCS) with a syphilis test between 2006 and 2018. The median registration year was 2007 [IQR (1999, 2013)] and the median year of birth was 1967 [IQR (1960, 1975)]. The key demographic characteristics of MSM_{wHD} in the SHCS is summarized in Table 1. There were 2665

Table 1. Characteristics of HIV-diagnosed MSM in the SHCS.

Variable	Value
Number of HIV-diagnosed MSM in the SHCS with at least one syphilis test between 2006 and 2018	5382
Total person-years of follow-up between 1st January 2006 and 31st December 2018	35375.7
Number of syphilis events observed during the observation period	2165
Median syphilis screening rate per person-year (IQR)	1.20 (1.02 to 1.58)
White ethnicity, n (%)	4855 (90.2)
Median year of birth (IQR)	1967 (1960 to 1975)
Median age at HIV infection (IQR)	35 (28 to 42)
Education level higher than high school, n (%)	2484 (46.2)
Nadir CD4 (IQR)	387.5 (272 to 533)
Ever used a recreational drug, n (%)	1246 (23.2)
Alcohol consumption more than once a month for at least 6 months during the entire follow-up, n (%)	4452 (82.7)
Current smoker, n (%)	2598 (48.3)
Ever had a non-steady partner, n (%)	3768 (70.0)
Ever had condomless anal intercourse with a non-steady partner, n (%)	1942 (36.1)

https://doi.org/10.1371/journal.pcbi.1009529.t001

and 4366 MSM$_{wHD}$ enrolled in the SHCS in 2006 and 2018, respectively. By assuming that 80% of MSM$_{wHD}$ in Switzerland are enrolled in the SHCS, we estimated the number of MSM$_{wHD}$ in Switzerland in 2006 and 2018 to be 3031 and 5257 [22,23]. We also estimated syphilis cases reported among MSM$_{wHD}$ in Switzerland in 2006 and 2018 to be 106 and 312, respectively.

Patterns of transmission risk

Information about reported non-steady partners and condomless anal intercourse was available for 5027 out of the analyzed 5382 MSM$_{wHD}$ (93.4%) enrolled in the SHCS during the observation period. 3768 out of 5027 MSM (75.0%) reported having a non-steady partner (nsP) at least once and 1942 (51.5%) among them reported condomless anal intercourse at least once. We estimated the proportion of MSM$_{wHD}$ with nsP to be 0.48 and 0.52 for the years 2006 and 2018, respectively (Fig C in S1 Text). We estimated that among MSM$_{wHD}$ the yearly rates of switching from without nsP to with nsP has decreased only slightly from 0.49 in 2006 to 0.41 in 2017. For the same period, we estimated that the yearly rates of switching back from with nsP to without nsP has decreased from 0.74 in 2006 to 0.45 in 2017 (Fig D in S1 Text). We estimated the proportion of MSM$_{w/oHD}$ with nsP to be 0.74 and 0.73 for the years 2006 and 2018 respectively using data published in *Gaysurvey* (Fig E in S1 Text) [25]. Our results were similar to the proportion of MSM$_{w/oHD}$ with nsP (0.75) published in European Men-who-have-sex-with-men Internet Survey (EMIS) 2017 [28]. As the *Gaysurvey* data is not longitudinal, we assumed a constant rate of switching for MSM$_{w/oHD}$ from without nsP to with nsP. It equaled the mean rate of switching for MSM$_{wHD}$ from without nsP to with nsP for the years 2006 and 2017 and estimated it to be 0.54. Based on the *Gaysurvey* data, we then estimated that the yearly rate of switching for MSM$_{w/oHD}$ from without nsP to with nsP has increased by 2.7% (1.44 in 2006 vs. 1.48 in 2017) (Fig F in S1 Text). Detailed information on the data used in our model is provided in the supplementary material (Tables A and B in S1 Text).

Observed and modelled data

The model could accurately reproduce the number of MSM$_{wHD}$ in Switzerland and the syphilis cases among MSM$_{wHD}$ and MSM$_{w/oHD}$ (Fig 2). The model estimated that the number of new
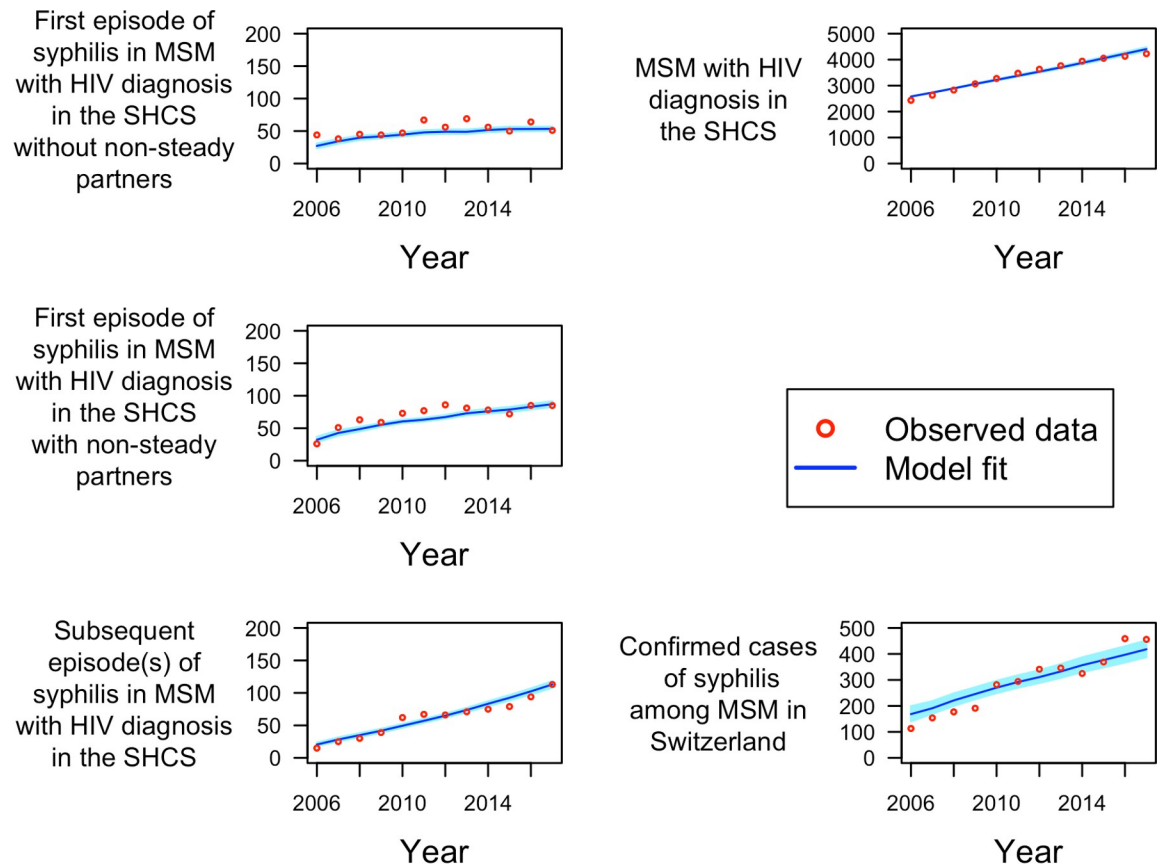
Fig 2. Model fit; MSM: men who have sex with men. SHCS: Swiss HIV Cohort Study; Red circles represents the observed datapoints obtained from the SHCS and literature. Blue line represents the median of the simplified Markov chain Monte Carlo (MCMC) model fit. Light blue shaded region represents the 95% quantile of the MCMC model fit.

https://doi.org/10.1371/journal.pcbi.1009529.g002

syphilis infections among MSM for the years 2006 to 2017 ranged between 168 and 418 diagnosed cases per year, which corresponds to an overall incidence rate of 2.24 and 4.91 syphilis cases per 1000 person-years (median syphilis incidence rate of 3.77 cases per 1000 person-years).

In addition, the model provided an estimate for the incidence rate of syphilis among MSM_{wHD} and $MSM_{w/oHD}$ stratified by reported non-steady partners (Fig 3). MSM_{wHD} had 45.93 [IQR (45.28, 46.32)] times the incidence of $MSM_{w/oHD}$, and MSM with non-steady partners had 1.63 [IQR (1.60, 1.67)] times the incidence of MSM without non-steady partners. Characterization of model optimization, model performance, and sampling for uncertainty estimates are depicted in the supplementary material (Figs G-K and Table C in S1 Text)

Counterfactual scenarios

We compared the incidence rate of syphilis obtained with the model fitted to the observed number of syphilis cases with simulations assuming the following alternative scenarios: firstly, we considered the impact of change in transmission risk between the years 2006 and 2018. With no change in the proportion of MSM switching from MSM with nsP to MSM without nsP and vice-versa between the years 2006 and 2018, we estimated a reduction of 17.56% (4.04 vs. 4.91 cases per 1000 person-years) in the incidence rate of syphilis in 2017 compared to incidence rate obtained by the model fit in 2017 (Fig L in S1 Text). Secondly, we considered the impact of change in screening frequency for syphilis between the years 2006 and 2018.
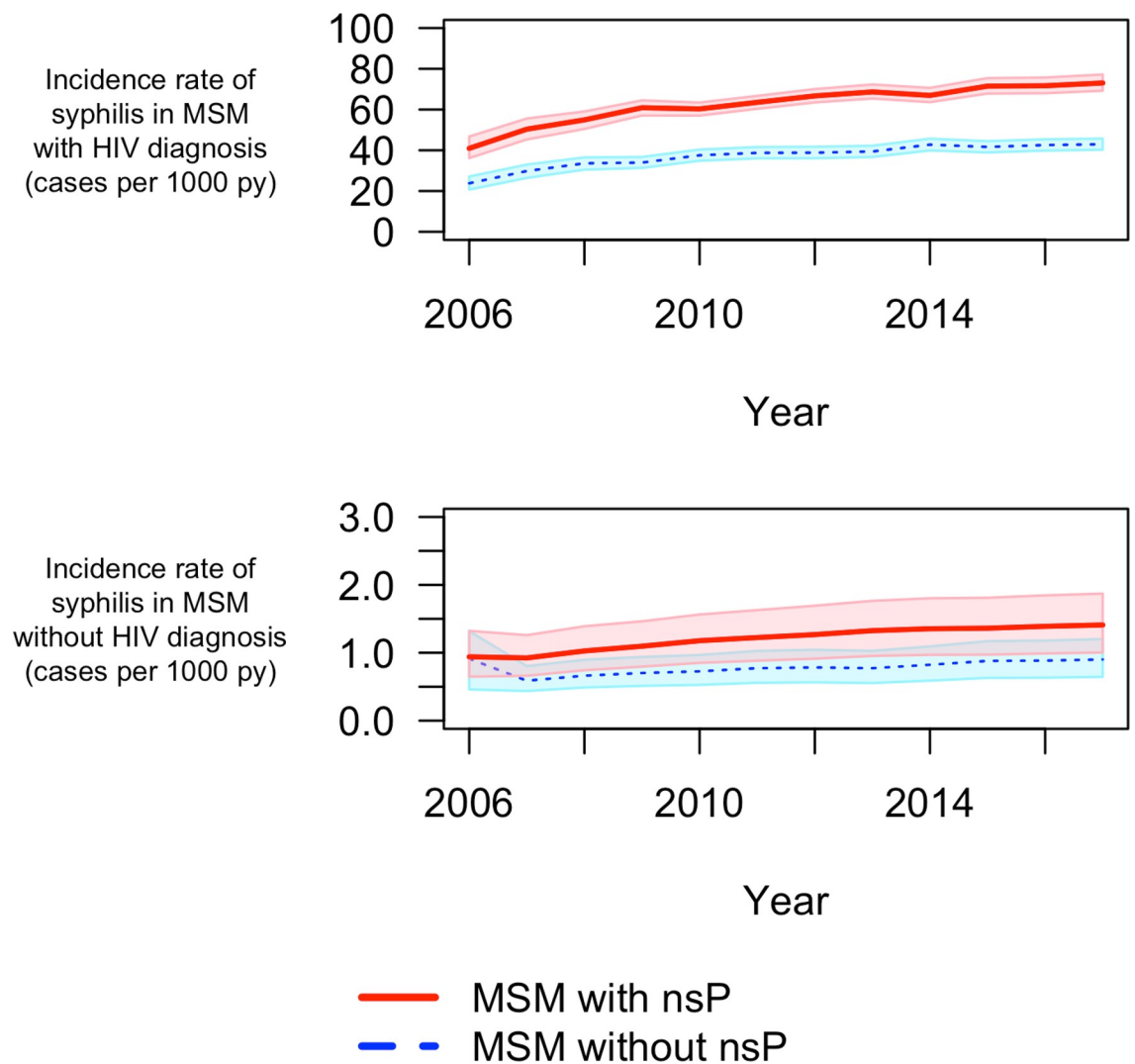
Fig 3. Model simulations–Incidence of syphilis stratified by transmission risk (reported non-steady partners) and HIV-status; MSM–men who have sex with men; nsP–non-steady partners; py–person-years; Solid red and dashed blue lines represent incidence rate of syphilis in MSM with and without nsP, respectively. The shaded regions represent the 95% quantile for the respective incidence rates.

https://doi.org/10.1371/journal.pcbi.1009529.g003

Increasing the frequency of screening for syphilis among MSM with HIV diagnosis and with nsP from once per year to twice per year during the observation period (corresponding to 48,576 syphilis screening tests instead of 24,179 tests), we estimated a reduction of 99.19% (0.04 vs. 4.91 cases per 1000 person-years) in the incidence rate of syphilis in 2017 compared to incidence rate obtained by the model fit in 2017. By contrast, we estimated only a reduction of 12.75% (4.28 vs. 4.91 cases per 1000 person-years) in the incidence rate of syphilis in 2017 by increasing the frequency of screening for syphilis among MSM without HIV diagnosis and with nsP from once per two years to twice per year during the observation period (corresponding to 1,289,070 syphilis screening tests instead of 332,226 tests) (Fig 4).
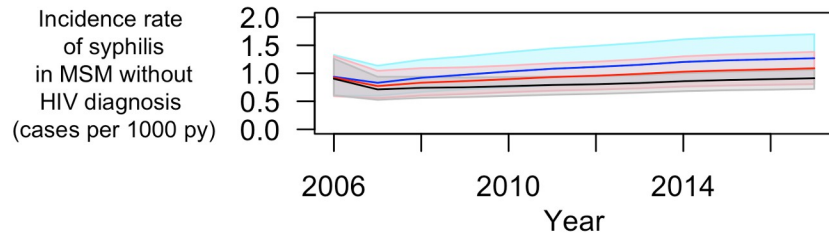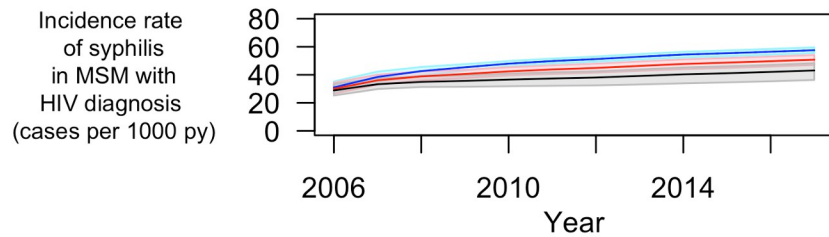
Sensitivity analysis

To test the robustness of the model and possible inconsistencies in data, we recalibrated the model and determined the corresponding change in the incidence rate of syphilis, the

a) Impact of syphilis screening frequency in MSM with HIV diagnosis (MSM$_{wHD}$)
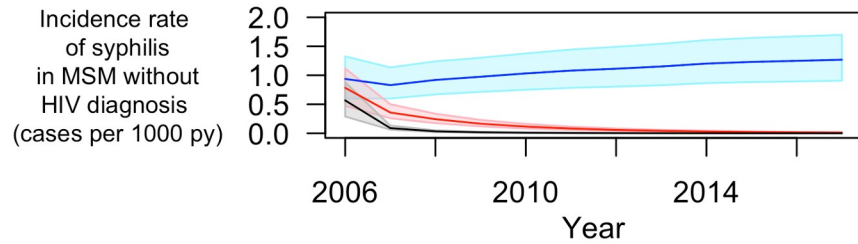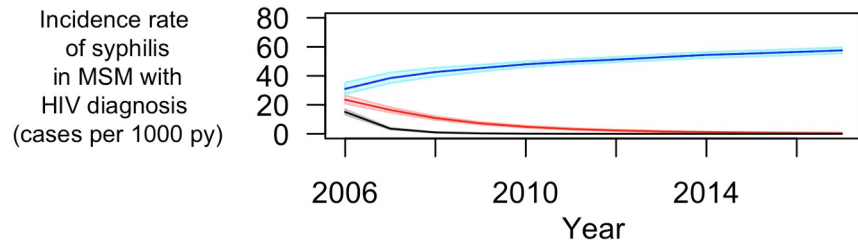
b) Impact of syphilis screening frequency in MSM without HIV diagnosis (MSM$_{w/oHD}$)

Fig 4. Counterfactual scenario: impact of change in screening frequency for syphilis. MSM–men who have sex with men; nsP–non-steady partners; py–person-years; Blue lines represent incidence rate of syphilis in the base model (initial model fit). Red and black lines in panel a) represent incidence rate of syphilis that obtained for the counterfactual scenarios when MSM with HIV diagnosis were screened for syphilis every 6 and 3 months instead of once a year, respectively. Red and black lines in panel b) represent incidence rate of syphilis that obtained for the counterfactual scenarios when MSM without HIV diagnosis were screened for syphilis every 6 and 3 months instead of once every 2 years, respectively. The shaded regions represent the 95% quantile for the respective incidence rates.

fitted parameters, and the goodness of fit (sum of squared weighted residuals) (Table D in S1 Text).

Firstly, we considered alternative criteria to stratify transmission risk (Fig M in S1 Text). When assuming reported non-steady condomless anal intercourse (nsCAI) as the transmission risk instead of nsP, we estimated that MSM with nsCAI had 1.71 [IQR (1.65, 1.81)] times the incidence of MSM without nsCAI. However, the goodness of fit for this model was considerably worse than for the main model (378.8 vs. 148.3). Secondly, we assessed the impact of the assumption of different transmission rates of syphilis among MSM_{wHD} and $MSM_{w/oHD}$. In the main model we had to assume different transmission rates, because of an apparent discrepancy in the data: despite similar frequency of reported nsP among MSM_{wHD} and $MSM_{w/oHD}$, we observed much higher incidence of syphilis among MSM_{wHD} than $MSM_{w/oHD}$ even when taking serosorting into account (Table B in S1 Text). To resolve this contradiction, in the main model, we assumed different transmission rates of syphilis (beta) in MSM_{wHD} and $MSM_{w/oHD}$ in our model (Table A in S1 Text). In the absence of this assumption, the model was unable to reproduce the syphilis epidemic in Switzerland and led to either a large overestimation of syphilis incidence in $MSM_{w/oHD}$ or a large underestimation in MSM_{wHD} (Fig N in S1 Text). As an alternative approach to capture the discrepancy in the data, we fitted a model assuming that there is no difference in transmission rate of syphilis among MSM_{wHD} and $MSM_{w/oHD}$ but instead including a parameter to account for possible underreporting of syphilis cases to FOPH among $MSM_{w/oHD}$ (Fig O in S1 Text). However, the goodness of fit for this model was worse than for the main model (sum of squared weighted residuals, 206.6 vs. 148.3) and required the assumption of an unrealistically high underreporting factor (40.8). Thirdly, we investigated the impact of a possible overestimation of transmission risk among $MSM_{w/oHD}$. We fitted models assuming the proportion of $MSM_{w/oHD}$ with nsP to be 25%, 50%, and 75% lower than the proportion of $MSM_{w/oHD}$ with nsP estimated from data published in the Gay-survey (Fig P in S1 Text). This corresponds to proportion of $MSM_{w/oHD}$ with nsP in 2017 to be 0.54, 0.36, and 0.18 vs. 0.73, respectively. The estimated goodness of fit values for these models were slightly better than the goodness of fit for the main model (136.4, 124.4, and 123.6 vs. 148.3 respectively) suggesting that model is robust to the hypothesized overestimation.

Fourthly, we assessed the impact of the duration of syphilis infectiousness on the dependency between the screening frequency and the syphilis incidence. Instead of assuming zero infectiousness in the latent stage of syphilis (>3 months since infection), we varied the infectiousness of syphilis in the latent stage to be 1% and 10% of that in the primary and/or secondary stage of syphilis (≤ 3 months since infection) (Fig Q in S1 Text). The goodness of fit values for these models were worse than for the main model (154.3 and 397.6 vs 148.3 respectively). As depicted above in the counterfactual scenario, increase in the frequency of screening for syphilis among MSM_{wHD} with nsP led to reduced simulated syphilis incidence in 2017. Increased infectiousness during the latent stage led to a smaller estimated reduction in syphilis incidence in 2017 in the counterfactual scenarios (93.59% and 63.50% vs. 99.19% by assuming the infectiousness in latent stage of syphilis to be 1% and 10% vs. 0% of that in primary and secondary stage of syphilis respectively) (Fig 5)

Fifthly, we tested the effect of using an alternative fitting procedure. Instead of fitting the model through minimization of the sum of squared weighted residuals, we fitted the model through maximization of the likelihood by assuming Poisson distributed incident cases of syphilis. We obtained similar median incidence rate and model fit as obtained by the main approach (Fig R in S1 Text).

Finally, we tested the robustness of our model by assessing if the model results were reliant on the choice of value of fixed parameters by sampling fixed parameter sets using Latin hypercube sampling followed by model optimization, and counterfactual scenario analyses (section

a) Impact of syphilis screening frequency for assuming 1% infectiousness in latent stage of that in primary and secondary stage of syphilis
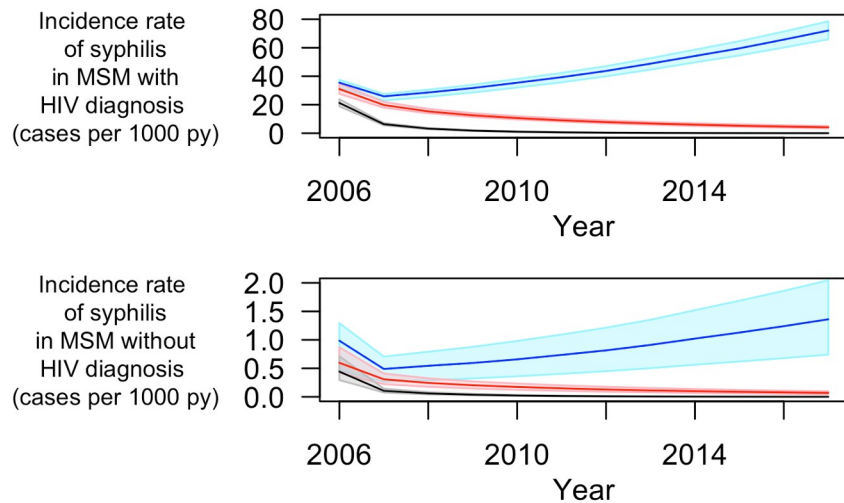
b) Impact of syphilis screening frequency for assuming 10% infectiousness in latent stage of that in primary and secondary stage of syphilis
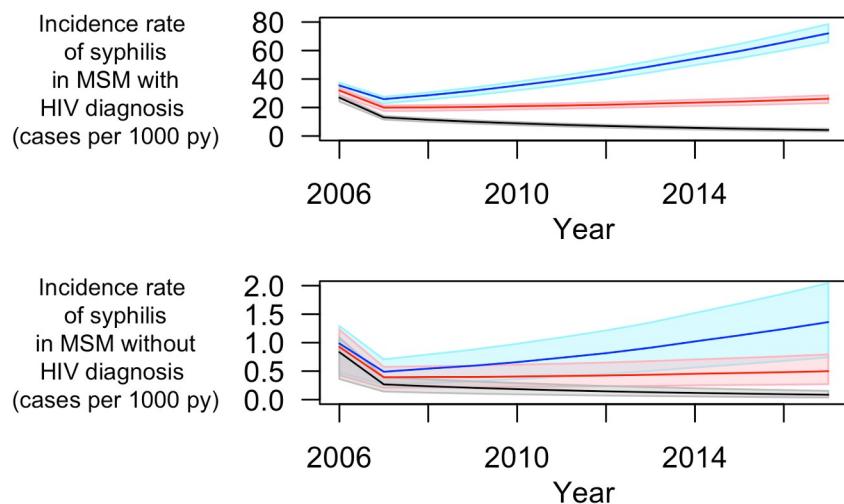
Fig 5. Sensitivity analysis: impact of allowing for syphilis transmission to occur in the latent stage. Panel a) and b) show the impact of syphilis screening frequency on syphilis incidence assuming the infectiousness of syphilis in the latent stage to 1% and 10% of that in primary and secondary stage of syphilis, respectively; MSM–men who have sex with men; nsP–non-steady partners; py–person-years; Blue lines represent incidence rate of syphilis in the base model (initial model fit). Red and black lines represent incidence rate of syphilis that obtained for the counterfactual scenarios when MSM with HIV diagnosis were screened for syphilis every 6 and 3 months instead of once a year, respectively. The shaded regions represent the 95% quantile for the respective incidence rates.

https://doi.org/10.1371/journal.pcbi.1009529.g005

11 in S1 Text). We found that our model results were robust to the choice of fixed parameter sets (Figs S and T in S1 Text).

Discussion

The transmission model we present was able to accurately reproduce the syphilis epidemic in Switzerland. Our study outlines the much higher incidence of syphilis in MSM with HIV diagnosis compared to MSM without HIV. In our simulations, MSM with HIV diagnosis have 46 times the syphilis incidence of MSM without HIV diagnosis. On average, MSM with non-steady partners (nsP) have 1.6 times the syphilis incidence in MSM without nsP. Also, constant yearly rates of switching from MSM without nsP to MSM with nsP (our measure of transmission risk) and vice-versa during the observation period would have led to a lower incidence of syphilis in 2017 by 17.6%. Finally, increasing the screening frequency of syphilis to twice per year in MSM with HIV diagnosis and with nsP would have contributed to a much higher reduction in syphilis incidence than increasing the screening frequency to twice per year in MSM without HIV diagnosis and with nsP (99.2% vs. 12.8%).

A key challenge in simultaneously modelling syphilis transmission in MSM_{wHD} and $MSM_{w/oHD}$ population is the apparent discrepancy in the data: when comparing the data from the FOPH and the SHCS, MSM_{wHD} exhibited 46 times the syphilis incidence of $MSM_{w/oHD}$, even though proportions of $MSM_{w/oHD}$ with nsP obtained from the data published in *Gaysurvey* was higher than the proportion of MSM_{wHD} with nsP estimated from the SHCS. To resolve this contradiction, we had to assume different transmission rates of syphilis in MSM_{wHD} and $MSM_{w/oHD}$ in our model. Based on fitting the model, we estimated a greater than 20-fold in transmission rate of syphilis in MSM_{wHD} compared to $MSM_{w/oHD}$, even after adjusting for contact probabilities and difference in screening frequency among MSM_{wHD} and $MSM_{w/oHD}$. As the majority of the MSM_{wHD} in Switzerland are virally suppressed, it is unclear whether a biological explanation for a higher transmission rate of syphilis in MSM_{wHD} is plausible. Alternatively, this difference may also be due to an unadjusted transmission risk of syphilis such as the number of partners and frequency of contacts, which we did not explicitly model.

To explore alternative distributions of risk, we stratified the structure of transmission risk in our model based on reported condomless anal intercourse with non-steady partners (versus reported non-steady partners). The model fit was worse than that in the main analysis. This might be because syphilis could be transmitted through oral sex, and using condoms for anal intercourses is not completely protective against syphilis [29]. In an alternative approach, we assumed no difference in transmission rate of syphilis among MSM_{wHD} and $MSM_{w/oHD}$ and allowed the model to account for possible underreporting of syphilis cases to FOPH among $MSM_{w/oHD}$ to explain the apparent difference in the incidence rate among MSM_{wHD} and $MSM_{w/oHD}$. We estimated the incidence of syphilis in $MSM_{w/oHD}$ to be 40.8 times that reported by FOPH. This hypothesized underreporting of syphilis cases, although not in the same magnitude, seems to be supported by the European Men-who-have-sex-with-men Internet Survey (EMIS) 2017 [28]. Based on the EMIS-2017 survey, 3.4% of all European $MSM_{w/oHD}$ and 13.9% of all European MSM_{wHD} (overall 4.4%) were diagnosed syphilis in the previous twelve months. If the EMIS-2017 were representative of MSM in Switzerland, the number of syphilis cases would have been about 6.3 times those reported to the FOPH. However, about 70% of the participants of EMIS-2017 were recruited through geosocial dating apps such as Planet-Romeo, Grindr, and Hornet. Several studies have shown that MSM who use geosocial dating apps have higher number of partners, frequency of unprotected sex, and incidence of sexually transmitted diseases compared to MSM who do not use such apps [30–33]. Hence,

the incidence of syphilis among participants of EMIS 2017 is likely higher than that in the overall MSM population in Switzerland.

Persons infected with syphilis are usually symptomatic during the primary and secondary stage of syphilis that lasts about 2–3 months since infection. After this period, individuals enter latent stage of syphilis during which they become asymptomatic, yet still detectable through syphilis screening. If left untreated, individuals can develop late/tertiary syphilis disease any time from 1 to 30 years after primary infection. About 25–40% of individuals with untreated syphilis can develop such diseases [34]. Hence, $MSM_{w/oHD}$ may be infected with syphilis but are not diagnosed due to lower frequency of syphilis screening and eventually may have non-syphilis related deaths, resulting in an underreporting of syphilis cases to FOPH. Moreover, despite syphilis being a notifiable disease, it is possible that not all cases are reported to the FOPH resulting in underreporting. However, the extent of underreporting is not clear and warrants further investigation.

Also, there is no clear evidence of the infectiousness of syphilis in the latent stage of syphilis (>3 months since infection) [13]. We tested the influence of infectiousness in the latent stage of syphilis. Our model could reproduce the syphilis epidemic for these scenarios and estimated similar incidence rates compared to the main model fit. By means of counterfactual scenarios, we further assessed the impact of infectiousness of syphilis in latent stage on the dependency between the screening frequency and the syphilis incidence. We found that the estimated reduction in syphilis incidence due to increase in screening frequency decreases when assuming residual infectiousness during the latent stage. Infectiousness during the latent stage of syphilis warrants further investigation as it may have an impact on the effectiveness of different screening strategies. However, even when we assumed infectiousness during the latent stage to be as high as 10% of that in primary and secondary stage, we observed 63.5% reduction in syphilis incidence in 2017 when screening of syphilis was performed twice per year instead of once per year in MSM_{wHD} with nsP. Our study results thus robustly indicate that frequent screening of MSM with HIV diagnosis and with nsP is required to curb syphilis transmission. This supports the EACS guidelines which recommend to "consider more frequent than annual screening if at risk" [35].

As mentioned before, we observed that the proportion of $MSM_{w/oHD}$ with non-steady partners is higher than the proportion of MSM_{wHD} with non-steady partners. On one hand, MSM_{wHD} in the SHCS answer the questionnaires on sexual behaviour during consultation or interviews with physicians or nurses they are likely to have recurrent contact with, while enrolled in the cohort. This may cause social desirability bias, thereby resulting in potential underestimation of transmission risk among MSM_{wHD}. On the other hand, MSM participating in *Gaysurvey* may not be representative of MSM in Switzerland, as MSM with nsP may be more likely to enroll in online surveys such as *Gaysurvey* compared to MSM without nsP, thereby resulting in an overestimation in transmission risk among $MSM_{w/oHD}$. We tested the influence of overestimation in transmission risk among $MSM_{w/oHD}$ estimated from data published from *Gaysurvey*. Our model could reproduce the syphilis epidemic for these scenarios and estimated similar incidence rates and similar goodness of fit compared to the main model fit indicating the robustness of our model. Finally, we fitted the model using maximization of likelihood by assuming Poisson distributed incident cases of syphilis and found similar results to that obtained by main model fit.

Our transmission model enabled us to integrate data from different sources such as published data from the FOPH and the literature, and the results estimated from the SHCS and cross-sectional studies to assess the drivers of the syphilis epidemic in Switzerland. Previous studies have shown the potential impact of more frequent screening in MSM for syphilis on reducing syphilis infections [17–20]. An individual-based mathematical model that simulates

the formation and breakup of sexual partnerships and tracks the transmission of syphilis within a synthetic population of sexually active gay men showed that increasing the frequency of syphilis screening can have a large impact on reducing syphilis prevalence [17]. The study also emphasized targeted frequent screening of gay men who have large numbers of partners or who engage in group sex to be a more efficient way of reducing syphilis transmission. An agent-based, network model of syphilis transmission, representing a core population of 2000 Canadian MSM at particular high risk for syphilis, explicitly estimated the effect of different screening frequencies on the projected annual rates of syphilis in this population [18]. The study showed that increased syphilis screening frequency was consistently more effective than improved coverage for screening. Our model differs from these studies, in that we not only focused on a core group of MSM by means of transmission risk of syphilis but also stratified the model based on HIV status. To the best of our knowledge, this is the first study to link the syphilis epidemic in MSM_{wHD} with that in $MSM_{w/oHD}$ and to estimate the effect of screening strategies implemented in target groups of the population on the overall epidemic.

One of the main limitations of our study is the uncertainty regarding the representativeness of the data used for $MSM_{w/oHD}$. This resulted in model assumptions which required critical sensitivity analyses to assess the robustness of our findings. Our study has however a substantial strength regarding HIV_{wHD}: the use of routine serological screening in a representative population over many years. The estimation of transmission risk of syphilis in MSM_{wHD} was based on the SHCS data. As the SHCS is highly representative for MSM_{wHD} in care in Switzerland, we expect these data to provide accurate estimates. In contrast, estimation of transmission risk in $MSM_{w/oHD}$ was based on cross-sectional studies which might have led to more uncertainty in our results. The degree of mixing between MSM_{wHD} and $MSM_{w/oHD}$ was based on the estimated frequency of HIV-discordant status in the data collected from VCT checkpoints across Switzerland where people can get spontaneously tested for sexually transmitted infections in a fully anonymized way. As bias towards screening upon transmission risk is expected, representativeness cannot be warranted. We stratified the model based on reported non-steady partners and condomless anal intercourse with non-steady partners as the transmission risk of syphilis. Although the available data in the SHCS did not allow us to account for the effect of other risk factors such as number of partners and frequency of sexual acts, the goodness of fit suggests reported non-steady partner to be a good proxy for risk stratification to model syphilis transmission.

In conclusion, our model reconstructed the syphilis epidemic among MSM in Switzerland by capturing changes in sexual risk behaviour and interactions between HIV MSM with and without HIV diagnosis. It suggests that having non-steady partners (nsP) regardless of condomless anal intercourse would be a suitable criterion for risk stratification when modelling syphilis transmission. More frequent screening and treating MSM with HIV diagnosis, particularly those with nsP may aid to curb syphilis transmission.

Supporting information

S1 Text. Supplementary information.
(PDF)

Acknowledgments

Author Contributions

Conceptualization: Suraj Balakrishna, Luisa Salazar-Vizcaya, Axel J. Schmidt, Andri Rauch, Roger D. Kouyos.

Data curation: Suraj Balakrishna, Katharina Kusejko.

Formal analysis: Suraj Balakrishna, Luisa Salazar-Vizcaya.

Funding acquisition: Andri Rauch, Roger D. Kouyos.

Investigation: Suraj Balakrishna, Luisa Salazar-Vizcaya, Roger D. Kouyos.

Methodology: Suraj Balakrishna, Luisa Salazar-Vizcaya, Axel J. Schmidt.

Project administration: Axel J. Schmidt.

Resources: Axel J. Schmidt, Maria Christine Thurnheer, Huldrych F. Günthard.

Software: Suraj Balakrishna, Viacheslav Kachalov.

Supervision: Andri Rauch, Roger D. Kouyos.

Validation: Suraj Balakrishna, Luisa Salazar-Vizcaya.

Visualization: Suraj Balakrishna, Luisa Salazar-Vizcaya.

Writing – original draft: Suraj Balakrishna.

Writing – review & editing: Luisa Salazar-Vizcaya, Axel J. Schmidt, Viacheslav Kachalov, Katharina Kusejko, Maria Christine Thurnheer, Jan A. Roth, Dunja Nicca, Matthias Cavassini, Manuel Battegay, Patrick Schmid, Enos Bernasconi, Huldrych F. Günthard, Andri Rauch, Roger D. Kouyos.

References

1. Public Health England. Sexually transmitted infections and chlamydia screening in England, 2016. Health Protection Report. 2016; 10(22).

2. Spiteri G, Unemo M, Mårdh O, Amato-Gauci AJ. The resurgence of syphilis in high-income countries in the 2000s: a focus on Europe. Epidemiol Infect. 2019;147. https://doi.org/10.1017/S0950268819000281 PMID: 30869043

3. Forrestel AK, Kovarik CL, Katz KA. Sexually acquired syphilis: Historical aspects, microbiology, epidemiology, and clinical manifestations. J Am Acad Dermatol. 2020; 82: 1–14. https://doi.org/10.1016/j.jaad.2019.02.073 PMID: 30986477

4. BAG-Bulletin 47. Federal Office of Public Health, Switzerland; 2018.

5. Thurnheer MC, Weber R, Toutous-Trellu L, Cavassini M, Elzi L, Schmid P, et al. Occurrence, risk factors, diagnosis and treatment of syphilis in the prospective observational Swiss HIV Cohort Study. AIDS Lond Engl. 2010; 24: 1907–1916. https://doi.org/10.1097/QAD.0b013e32833bfe21 PMID: 20616699

6.   Shilaih M, Marzel A, Braun DL, Scherrer AU, Kovari H, Young J, et al. Factors associated with syphilis incidence in the HIV-infected in the era of highly active antiretrovirals. Medicine (Baltimore). 2017; 96: e5849. https://doi.org/10.1097/MD.0000000000005849 PMID: 28079818

7.   Roth JA, Franzeck FC, Balakrishna S, Lautenschlager S, Thurnheer MC, Trellu LT, et al. Repeated Syphilis Episodes in HIV-Infected Men Who Have Sex With Men: A Multicenter Prospective Cohort Study on Risk Factors and the Potential Role of Syphilis Immunity. Open Forum Infect Dis. 2020; 7. https://doi.org/10.1093/ofid/ofaa019 PMID: 32016128

8.   Wu MY, Gong HZ, Hu KR, Zheng H-Y, Wan X, Li J. Effect of syphilis infection on HIV acquisition: a systematic review and meta-analysis. Sex Transm Infect. 2020; sextrans-2020-054706. https://doi.org/10.1136/sextrans-2020-054706 PMID: 33219164

9.   Hook EW. Syphilis. The Lancet. 2017; 389: 1550–1557. https://doi.org/10.1016/S0140-6736(16)32411-4

10. Polansky A, Levy I, Mor Z. Risk factors of syphilis co-infection among HIV-infected men who have sex with men in Tel-Aviv, Israel. AIDS Care. 2019; 31: 1157–1161. https://doi.org/10.1080/09540121.2019.1612006 PMID: 31035774

11. Stoltey JE, Cohen SE. Syphilis transmission: a review of the current evidence. Sex Health. 2015; 12: 103–109. https://doi.org/10.1071/SH14174 PMID: 25702043

12. Kouyos RD, Hasse B, Calmy A, Cavassini M, Furrer H, Stöckle M, et al. Increases in Condomless Sex in the Swiss HIV Cohort Study. Open Forum Infect Dis. 2015;2. https://doi.org/10.1093/ofid/ofv077 PMID: 26180827

13. Workowski KA, Bolan GA. Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep. 2015; 64: 1–137. PMID: 26042815

14. Moore MB, Price EV, Knox JM, Elgin LW. Epidemiologic treatment of contacts to infectious syphilis. Public Health Rep. 1963; 78: 966–970. PMID: 14084872

15. Schroeter AL, Turner RH, Lucas JB, Brown WJ. Therapy for incubating syphilis. Effectiveness of gonorrhea treatment. JAMA. 1971; 218: 711–713. PMID: 5171497

16. Burchell AN, Tan DHS, Grewal R, MacPherson PA, Walmsley S, Rachlis A, et al. Routinized Syphilis Screening Among Men Living With Human Immunodeficiency Virus: A Stepped Wedge Cluster Randomized Controlled Trial. Clin Infect Dis. 2021 [cited 13 Aug 2021]. https://doi.org/10.1093/cid/ciab582 PMID: 34175944

17. Gray RT, Hoare A, Prestage GP, Donovan B, Kaldor JM, Wilson DP. Frequent testing of highly sexually active gay men is required to control syphilis. Sex Transm Dis. 2010; 37: 298–305. https://doi.org/10.1097/OLQ.0b013e3181ca3c0a PMID: 20393383

18. Tuite AR, Fisman DN, Mishra S. Screen more or screen more often? Using mathematical models to inform syphilis control strategies. BMC Public Health. 2013. https://doi.org/10.1186/1471-2458-13-606 PMID: 23800206

19. Saad-Roy CM, Shuai Z, van den Driessche P. A mathematical model of syphilis transmission in an MSM population. Math Biosci. 2016; 277: 59–70. https://doi.org/10.1016/j.mbs.2016.03.017 PMID: 27071977

20. Iboi E, Okuonghae D. Population dynamics of a mathematical model for syphilis. Appl Math Model. 2016; 40: 3573–3590. https://doi.org/10.1016/j.apm.2015.09.090

21. Population data, 1950–2018. Federal statistical office, Switzerland; 2019. Available: https://www.bfs.admin.ch/bfs/en/home/statistics/population.assetdetail.9466635.html

22. Schmidt AJ, Altpeter E. The Denominator problem: estimating the size of local populations of men-who-have-sex-with-men and rates of HIV and other STIs in Switzerland. Sex Transm Infect. 2019 [cited 15 Jun 2020]. https://doi.org/10.1136/sextrans-2017-053363 PMID: 30679393

23. Kohler P, Schmidt AJ, Cavassini M, Furrer H, Calmy A, Battegay M, et al. The HIV care cascade in Switzerland: reaching the UNAIDS/WHO targets for patients diagnosed with HIV. AIDS Lond Engl. 2015; 29: 2509–2515. https://doi.org/10.1097/QAD.0000000000000878 PMID: 26372488

24. Swiss HIV Cohort Study, Schoeni-Affolter F, Ledergerber B, Rickenbach M, Rudin C, Günthard HF, et al. Cohort profile: the Swiss HIV Cohort study. Int J Epidemiol. 2010; 39: 1179–1189. https://doi.org/10.1093/ije/dyp321 PMID: 19948780

25. Lociciro S, Bize R. Les comportements face au VIH/Sida des hommes qui ont des rapports sexuels avec des hommes. Enquête Gaysurvey 2014. Lausanne, Institut universitaire de médecine sociale et préventive, 2015 (Raisons de santé 253).

26. R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

27. Soetaert K, Petzoldt T. Inverse Modelling, Sensitivity and Monte Carlo Analysis in R Using Package FME. J Stat Softw. 2010; 33: 1–28. https://doi.org/10.18637/jss.v033.i03 PMID: 20808728

28. EMIS-2017 –The European Men-Who-Have-Sex-With-Men Internet Survey. In: European Centre for Disease Prevention and Control [Internet]. 29 Aug 2019 [cited 15 Jun 2020]. Available: https://www.ecdc.europa.eu/en/publications-data/emis-2017-european-men-who-have-sex-men-internet-survey

29. Ficarra G, Carlos R. Syphilis: The Renaissance of an Old Disease with Oral Implications. Head Neck Pathol. 2009; 3: 195–206. https://doi.org/10.1007/s12105-009-0127-0 PMID: 20596972

30. Beymer MR, Weiss RE, Bolan RK, Rudy ET, Bourque LB, Rodriguez JP, et al. Sex on demand: geosocial networking phone apps and risk of sexually transmitted infections among a cross-sectional sample of men who have sex with men in Los Angeles County. Sex Transm Infect. 2014; 90: 567–572. https://doi.org/10.1136/sextrans-2013-051494 PMID: 24926041

31. Eaton LA, Maksut JL, Gamarel KE, Siembida EJ, Driffin DD, Baldwin R. Online Sex Partner Meeting Venues as a Risk Factor for Testing HIV Positive Among a Community-Based Sample of Black Men Who Have Sex With Men. Sex Transm Dis. 2016; 43: 360–364. https://doi.org/10.1097/OLQ.0000000000000454 PMID: 27200520

32. Chan PA, Crowley C, Rose JS, Kershaw T, Tributino A, Montgomery MC, et al. A Network Analysis of Sexually Transmitted Diseases and Online Hookup Sites Among Men Who Have Sex With Men. Sex Transm Dis. 2018; 45: 462–468. https://doi.org/10.1097/OLQ.0000000000000784 PMID: 29465663

33. Hoenigl M, Little SJ, Grelotti D, Skaathun B, Wagner GA, Weibel N, et al. Grindr Users Take more Risks, but are more Open to HIV Pre-Exposure Prophylaxis: Could this Dating App Provide Platform for HIV Prevention Outreach? Clin Infect Dis Off Publ Infect Dis Soc Am. 2019. https://doi.org/10.1093/cid/ciz1093 PMID: 31677383

34. Hicks BC, Clement M. Syphilis: Epidemiology, pathophysiology, and clinical manifestations in HIV-uninfected patients. Available: https://www.uptodate.com/contents/syphilis-epidemiology-pathophysiology-and-clinical-manifestations-in-hiv-uninfected-patients

35. Ryom L, Cotter A, Miguel RD, Béguelin C, Podlekareva D, Arribas JR, et al. 2019 update of the European AIDS Clinical Society Guidelines for treatment of people living with HIV version 10.0. HIV Med. 2020; 21: 617–624. https://doi.org/10.1111/hiv.12878 PMID: 32885559