The *Syphilis Interventions towards Elimination (SITE)* model projecting epidemic impact and cost of syphilis prevention and treatment interventions – technical methods report

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SUMMARY

Background: Eliminating syphilis as a public health problem has been a commitment of many countries and international organizations, often not realized.

Methods: We developed a compartmental model of syphilis transmission within adult populations, comprising 7 risk groups, to inform syphilis control strategies and target setting. Model structure, methods and assumptions were designed based on the national HIV planning model Spectrum Goals. We present scenario results, calibrated to published epidemiological, behavioural and program data, for Papua New Guinea (PNG) and Peru as examples of high-transmission and moderate-transmission settings (prevalence of active syphilis in 2019: 2.0% and 0.89%, respectively).

Results: In simulations, enhanced symptom-driven treatment reaching the early, infectious stage of infection reduced incidence by 52% in Peru or 84% in PNG in 2030, relative to simulations with constant coverage as in 2018. Contact tracing and treatment amplified this impact to 62% and 88%, respectively. Population screening reduced overall population incidence by 7-34% depending on targeted high-risk groups and setting.

Elimination – defined by the World Health Organization as a 90% reduction in infection incidence from 2018 to 2030 – was feasible in both countries, when combining symptom-driven case management, including contact tracing, with outreach prioritizing highest-risk key groups for condom promotion and syphilis screening.

Conclusions: In both countries, elimination requires several-fold increases in service coverage and investment; the feasibility of such scale-up remains to be assessed. Despite uncertainties in sexual network patterns, some natural history parameters and baseline treatment coverage and antibiotic exposure rates, the model provides an analytical framework and user-friendly tool for supporting the development of country-tailored programs.

Abbreviations:

ANC = antenatal care; FSW = Female Sex Worker; (I)BBS = (Integrated) Bio-Behavioural Survey; DHS = Demographic and Health Survey; MSM = Men having sex with men; PNG = Papua New Guinea; PrEP = pre-exposure prophylaxis; RPR = Rapid Plasma Reagin test; STI = sexually transmitted infection; TPHA = Treponema pallidum hemagglutination assay; TPPA = Treponema pallidum particle agglutination assay; VDRL = Venereal Disease Research Laboratory; WHO = World Health Organization.

List of Annexes / supplementary materials:

Annex 1. Model description
Annex 2. Contact tracing intervention
Annex 3. Prevalence data
Annex 4. Sensitivity analyses: parametrizations and detailed results

INTRODUCTION

Syphilis is a common, curable sexually transmitted infection (STI). Untreated, the infection persists for many years and causes significant morbidity, added risk of HIV transmission, as well as high rates of adverse pregnancy outcomes. Syphilis elimination should be attainable and cost-effective, including in low-income settings, as the infection has no known animal reservoir, can be diagnosed and cured with simple, inexpensive tests and drugs [1].

In past decades, syphilis control programs have brought down infection rates, by targeted testing and treatment. However, in recent years outbreaks occurred in several countries, in the Americas (USA, Argentina, Brazil), Asia [2, 3] and including resource-rich countries [4], in particularly among men who have sex with men (MSM) and young people. At global level, syphilis is estimated to have remained equally prevalent in 2016 as in 2012 [5-7], whereas the World Health Organization (WHO) Global Health Sector Strategy on STIs 2016-2021 formulated the goal to reduce incidence of *Treponema pallidum* over 2018–2030 by 90% [8, 9].

Importantly, the persistently high infection rates of syphilis in pregnant women [1] threatens national and global efforts to eliminate congenital syphilis. The WHO, the Pan-American Health Organization, the WHO Western Pacific Regional office and many countries have committed to eliminating congenital syphilis, often in the context of dual or triple elimination efforts alongside congenital HIV and hepatitis [10-13]. As of April 2020, 13 countries have been validated by the WHO as having eliminated mother-to-child transmission of syphilis; yet worldwide, progress falls far short of the global WHO target that 80% of countries eliminate syphilis mother-to-child transmission by 2030 [8].

Barriers to syphilis control and elimination include health services capacity and access (which is lower among men), stock-outs of penicillin and syphilis rapid tests, and sometimes organizations beset by inefficiencies, fragmentation and outdated technology. Eliminating syphilis in a country requires a well-coordinated and targeted response, that can draw on strong health systems and supportive community engagement and reliable surveillance and program monitoring. Key programmatic challenges are reaching the key populations and ensuring all those diagnosed are promptly and appropriately treated.

HIV combination prevention interventions offer a renewed opportunity to advance towards syphilis elimination, by integrating services. Some authors have suggested that the widespread availability of antiretroviral therapy and HIV pre-exposure prophylaxis (PrEP) may result in lower condom use and resurgence of STI transmission [14, 15]. The infrastructure of ART and PrEP services, however, also provides opportunities for syphilis prevention, screening and treatment.

To support the WHO Americas and Western Pacific regions and national STI programs in establishing targets, epidemiological frameworks and cost-effective program strategies for syphilis elimination, we developed a dynamical model of adult syphilis transmission, with a structure that matches typical national surveillance and program data, performance monitoring indicators and strategy targets. This report presents its design, methods and assumptions. Projections for example countries Papua New Guinea (PNG) and Peru (based on desk review of published studies) show the health impact, service levels and cost of various scale-up packages of prevention, screening and treatment interventions.

METHODS

Model: structure and sexual behaviour

The Syphilis Interventions Towards Elimination (SITE) model is compartmental, dividing the adult population into groups based on risk behaviour, as in the Spectrum Goals model of HIV transmission,

which is used by over 40 low- and middle-income countries for national HIV/AIDS strategic planning [16]. The population structure matches commonly available country specific behavioural and epidemiological HIV/STI surveillance data, thus facilitating country calibration against national HIV and syphilis data.

National population sizes were taken from the 2017 World Population Prospects, 2015-2020 estimates and 2015-2030 projections in the medium (i.e. intermediate-growth) variant [17]. The 15-49 years-old population is divided into seven risk groups, reflecting a gradient of risk (Annex 1):

- Low-risk men and women, who have 1 stable heterosexual partnership throughout the year;
- Medium-risk women and men, who have multiple shorter-duration partnerships within a year (and in addition may or not be married to a low-risk heterosexual person);
- High-risk women and men, i.e. Female Sex Workers (FSW) and their male clients;
- MSM, who mix within MSM; a small proportion being married to a low-risk woman.

In addition, modelled groups include non-sexually active men and women, representing young adults before sexual debut and strictly monogamous couples at zero risk of infection.

The model was programmed in C++ as an add-on package of R, version 3.5.1 [18]. User-defined parameter input values are specified in an Excel file, as are model outputs. It runs over 1970-2050, in weekly time steps.

Natural history

Syphilis natural history is based on the STI model for South Africa [19], triangulating with other adult transmission models and reviews [20-28] and assumptions used in WHO global estimates [7, 29, 30].

The model distinguishes 6 infection stages (Figure 1). Susceptible individuals acquire infection (move from Compartment 0 to 1) at a rate λ that depends upon the probability of transmission per sexual contact, the number of partners, acts per partner, condom use and the probability of encountering an infectious partner (Annex 1).

If not treated, infected individuals move from incubation stage (Compartment 1) to primary/ secondary syphilis (Compartment 2), then latent syphilis (Compartment 3). We combined primary and secondary syphilis, as diagnostic tests used for screening do not distinguish between these stages and evidence is limited regarding differential infectivity.

Rates of movement between stages reflect average stage duration (Table 1) and the coverage of treatment. In addition to symptom-driven clinical treatment (exiting from Compartment 1 to Compartments 4 and 6) and screening-based treatment (exiting to Compartment 4), we assumed that individuals in latent stage may inadvertently get cured (moving to Compartment 5) when treated for other infections with an antibiotic effective against syphilis. Ultimately, all individuals who are cured become susceptible to reinfection, at the same rate as those who have never been infected (Compartment 6).

In the model only individuals with primary/secondary infection (Compartment 2) are infectious. Transmission is modelled via probabilities per sex act, which apply during Primary/Secondary stage. Values were fitted within plausible ranges (Table 1a).

Interventions

The model includes the following interventions, with coverage variable by risk group:

- **Screen and treat** using either a non-treponemal, e.g. Rapid Plasma Reagin (RPR)) test, or a treponemal (TPHA or TPPA-based) test, or a dual algorithm including both non-treponemal and treponemal tests – followed by treatment of those found positive. Effectiveness depends on the infection stage at detection, and the test algorithm. For any screening test used:
    - Primary/Secondary infection (Compartment 2): 40% become RPR-negative and susceptible to reinfection immediately (Compartment 6); the remainder become temporarily immune to reinfection, remaining RPR-positive during that period (Compartment 4);
    - Latent stage (Compartment 3): 100% are temporarily RPR-positive and immune to reinfection (Compartment 4);
    - Recovered but not yet susceptible (Compartments 4 and 5): 100% get diagnosed and treated again, but they remain where they are with unchanged duration [19, 21].

  Additionally, screening using TPHA without RPR confirmation also diagnoses and (re-)treats people in Compartment 6, without any health effect.

- **Symptom-driven, clinical treatment following care seeking for symptoms during primary/secondary infection:** 60% of individuals in the primary/secondary stage were assumed to be symptomatic. Of those symptomatic patients who get treated effectively 40% become RPR-negative and susceptible to reinfection (Compartment 6) immediately [19]; the others also recover and become non-infectious, but remain temporarily RPR-positive and immune to reinfection (Compartment 4).

Treatment of individuals with symptomatic Primary/Secondary infection, and those with Primary/Secondary or Latent infection detected by screening, are both assumed to be 90% effective (Table 1a).

- **Contact referral, testing and treatment,** of partners of patients treated clinically for symptomatic Primary/Secondary syphilis. Tracing results in treatment if the contact is diagnosed with Primary/Secondary infection. Contacts traced are assumed to come proportionally from all groups of sexual partners, except that FSW and their clients do not refer each other (Annex 2). Prevalence among contacts is calculated dynamically, assuming that the majority of contacts traced would most typically have been infected by the index case (and not the reverse order) – considering the types of partners referred (with a user-editable parameter indicating the chance that index patients refer their source partners rather than low-risk other partners), the duration of Primary/Secondary infection until treatment in the index case and until referral of the contact, and the frequency of sex acts and per-act transmission probability for the given type of partner referred. Resulting yield, i.e. prevalence among contacts, is an output which the user can compare and re-calibrate if program data exist on contact tracing numbers and yields.

- **Condom usage**: The model distributes usage randomly over all relationships and contacts (within each combination/pair of risk groups).

- Reductions in the rate of **sexual partner change**.

Country calibrations

The model was applied to PNG and Peru. Both countries have existing Spectrum Goals models of the national HIV epidemic [31], good-quality comprehensive public syphilis prevalence data across lower-risk and higher-risk groups over multiple years, and published data on coverage of syphilis screening and symptom-driven clinical treatment, for different groups.

Prevalence: Prevalence for low-risk and medium-risk women was fitted (manually) to sentinel surveys and/or routine program screening data on pregnant women visiting Ante-Natal Care (ANC) [5, 32]. Simulations for FSW and MSM were fitted to Integrated Bio-Behavioural Surveys (IBBS) and other published surveys (Annex 3). When fitting the prevalence data, prevalence data from studies that did not use both a treponemal and a non-treponemal test were adjusted to a corresponding prevalence of RPR+/TPHA+ dual positivity, as in the WHO global and Spectrum-STI country estimates [7, 29, 30].

Sexual risk behaviours: Risk group sizes and behavioural parameters were fitted to survey data (Table 1b), considering their values from Goals calibration [16] of the national HIV epidemic [31].

Screening and treatment coverage: Screening and treatment coverage for each risk group were based on numbers of people screened and/or treated divided by national size estimates (e.g. FSW, or ANC women). For groups without such data, pre-2019 screening coverage was set within the range of 15-25% for MSM and FSW, and 3-6% for other groups – with the precise value adjusted to reproduce group-specific prevalence data, and considering WHO estimation assumptions:
For symptom-driven clinical treatment, we set baseline coverage at 25% for low-risk women, 35-40% for other groups in PNG and 50-60% for other groups in Peru. The higher coverage in Peru matches relative coverages assumed in WHO's global and regional STI estimates [7, 29, 30]) for countries of low and moderate treatment access, respectively. At the assumed treatment coverages (Table 1b), the model estimated that 753 women and 1,228 men would have been clinically treated for syphilis in 2018 in PNG, and 1,283 women and 3,493 men in Peru. PNG implements syndromic STI management, hence cases reported are Genital Ulcer Disease, of which only few are typically caused by syphilis. Also from Peru we lacked program data on clinically treated, etiologically confirmed syphilis cases for comparison. As alternative point of reference, the baseline coverages correspond to cumulative treatment rates in line with the WHO-estimated 75-85% of latent cases that cumulatively get treated before progressing into tertiary syphilis, in countries with poor or moderate treatment access [29]: in 2018, 77-90% of new infections were projected to have been treated (clinic-based or following screening) in Peru, and 79-81% in PNG.

Intervention scenarios and impact assessment
We simulated 15 interventions and intervention combinations (Table 2). In all scenarios, scale-up started in 2019, at the targeted coverage immediately, and maintained throughout the projection.

Impact was evaluated considering national-level incidence reductions over 2019-2030, and compared to the elimination goal to reduce incidence rates by 90% from 2018 to 2030, of the WHO global STI health sector strategy [8].

Cost and cost-effectiveness
Intervention scenarios were costed applying unit costs (per test, treatment, condom, or contact traced) to volumes of services. Cost-effectiveness was assessed as cost (in US$) per infection averted, over 2019-2030. No discounting was applied to either cost or infections.

RESULTS

Epidemic fit
Both countries had considerable data from ANC women & FSW, spanning the period 1988-2017 in Peru and 1989-2017 in PNG (Figure 2; Annex 3). Prevalence in all groups was higher in PNG than Peru. For men, both countries had prevalence data from community surveys and blood donors, but they lacked standardized periodic measurements to accurately indicate time trends. Model fitting suggested that in both countries prevalence of syphilis has been falling in all populations (Figure 2).

The model projections of prevalence in lower-risk adults, male FSW clients and MSM were all lower in Peru than in PNG (Figure 2) reflecting Peru's higher coverage of clinical treatment and ANC-based screening, earlier adoption of condom usage by FSW/clients and MSM (Table 1b) and that commercial sex is less common in Peru than in PNG (Table 1b).

For FSW, the model replicated marked declines in prevalence observed post-2000 in both PNG and Peru (Figure 2 & Annex 3) – precipitated by increased condom use (Table 1b), also believed to have driven historic declines in HIV [31, 33, 34]. Also for MSM, the model estimated syphilis declines over 2000-2018 – in line with HIV incidence trends [31, 33]. However, in both countries the number of data points on MSM were limited and the populations of MSM sampled were not consistent. Specifically, in PNG there were only two data points from MSM (2010 and 2016); and while these suggest a decline over time, the first data point is from MSM who sell sex, a sub-population with possibly higher risk (Annex 3). In Peru, early studies may have over-sampled higher-risk MSM whereas in PNG high-risk MSM were not reached due to high levels of stigma [35].

Modelled declines in prevalence among FSW and MSM drove parallel prevalence declines in lower-risk groups, in men and women in both countries. In Peru, this decline is supported by ANC surveillance and routine data, whereas PNG's ANC data did not indicate any clear trend (Figure 2).

In both countries, overall prevalence was higher in men than in women, due to large groups of high-risk men i.e. FSW clients with high prevalence (Table 3). The male-to-female prevalence ratio is higher than the 1.0 found in a national survey in Peru in 2000 [36] or previous estimates for other countries [37-39]. We found no representative population-based male prevalence data from either country to corroborate overall male prevalence.

In PNG, the group with highest prevalence in 2018 was MSM; yet most new cases occurred in high-risk men (clients of FSW) and medium-risk men and women, groups with a relatively high prevalence and large size (Table 3a). However, over 1970-2005, prior to condom adoption and increasing screening coverage, FSW had highest prevalence. Peru showed similar patterns (Table 3b), although with a lower share of medium-risk women in incidence – reflecting that risk behaviours are less widespread than in PNG.

In both countries, FSW and MSM were estimated to represent 1-2% of adult women and 2-3% of adult men, yet account for 7% and 13-21% of incident cases, respectively, making them an important target group for syphilis interventions. The importance of these two groups is further illustrated by the stage distribution of prevalent cases (Figure 3). MSM and FSWs not only have the highest overall prevalence of the seven population groups, but also – and by far -- the highest prevalence of primary and secondary stage syphilis (red bars in Figure 3), the unique infectious stage that drives transmission in the overall population. This pattern is visible in both Peru and PNG and can be seen in the point prevalence (Figure 3a and 3c) and the relative share of primary and secondary stage within overall syphilis prevalence (Figure 3b and 3d). The relatively high prevalence of primary and secondary stage syphilis in FSW and MSM reflects not only their high exposure but also their relatively good access to syphilis screening and treatment which renders them susceptible to re-infection.

Intervention and program impact

Of interventions modelled, clinical treatment of symptomatic Primary/Secondary cases had the largest impact (Figure 4a+b). Especially in PNG, with low baseline treatment coverage and high background incidence, enhancing treatment coverage to levels typical for medium-access countries [30] could by itself almost reduce syphilis incidence by 90% by 2030 (Figure 4a). Clinical treatment is the one intervention specifically targeting the symptomatic, infectious stage of syphilis; at the modelled 60% coverage (of

60% of cases that are symptomatic) it removes effectively up to half of the infectious cases, thus suppressing the transmission cycle.

Screening also contributed to reducing incidence, if targeted to FSWs and offered at least yearly. In contrast, screening only low- and medium-risk adults was much less effective (Table 4), irrespective of frequency (scenarios not shown).

Of note, the impact of screening is a composite effect of detecting and treating some infectious (Primary/Secondary-stage) and many more latent cases, who then move (via recovered, temporarily immune) to being susceptible to reinfection, which increases subsequent incidence. The latter counterproductive effect reduces impact of screening, relative to clinical treatment, which reaches more infectious (Primary/Secondary-stage) cases.

Condom usage in FSW contacts very effectively lowered syphilis transmission (at 2030, relative to the Constant coverage scenario: reduced by 30% in PNG and 35% in Peru), and at the assumed coverage increases, more so than FSW screening (which produced incidence reductions of 18% and 22%, respectively).

Screening or improved condom usage by MSM had little overall impact beyond this group, which is relatively small and isolated, in PNG; but a larger impact in Peru, with a larger MSM population with higher heterosexual marriage rate.

Among clinical interventions, contact tracing magnified treatment impact, provided it reached infected contacts (Figure 4c+d). Among contacts traced, prevalence ranged from 25-52% in PNG and 21-40% in Peru. In both countries, this yield was higher in scenarios with lower baseline treatment coverage and thus higher background prevalence. The modelled ranges align with tracing yields observed in field programs (Annex 2) and well exceeds background prevalence in populations modelled.

Combining interventions at stipulated coverage targets in an elimination scenario was predicted to achieve elimination. A medium-term scenario, with more realistic coverages, would also just achieve elimination in both countries, as would increasing condom usage in by FSW, MSM and medium-risk groups (without scale-up treatment or screening).

Regardless of intervention or package, proportional impact was typically larger in Peru compared to PNG, due to Peru's lower baseline incidence, which makes elimination easier. An exception is treatment of symptomatic cases, for which PNG had much lower baseline coverage, such that scale-up to the common coverage target achieved relatively larger impact than Peru (Figure 3, red lines).

Cost & Cost-effectiveness

At notional service unit costs (identical for both countries; Table 4), clinical treatment of symptomatic cases costed least per infection averted (Table 4). Contact tracing enhanced cost-effectiveness, especially at higher treatment coverages.

Screening of FSW and MSM, and condom promotion also had relatively low cost per infection averted. Blanket screening of low-risk and medium-risk adults was much less cost-effective, especially in Peru with low prevalence in these groups.

Combination packages at high coverage, while impactful, were slightly less cost-effective, due to saturation effects: screening diminishes marginal returns once other interventions have lowered prevalence. The Elimination scenario was thus less cost-effective than the Medium-term package.

Sensitivity analyses

Four univariate sensitivity analyses examined key uncertainties in model structure and parametrization.

A first variant assumed lower rates of incidental cure, with an average duration of Latent syphilis, absent program-based treatment, of 40 years instead of the default 15 years. In this variant, baseline (default) incidence rates were 20% lower in both countries. Impacts on incidence were stronger for any intervention, without notable change in ranking across interventions (Annex 4a).

Second, we changed natural history to refit prevalence data under a shorter or longer duration of the infectious (primary + secondary) stage, offset by higher transmission probabilities. These alternative calibrations, however, failed to reproduce adequate fit to prevalence data, hence we did not pursue them.

Two other analyses explored alternative sexual mixing structures. This was motivated by the observation that the default model gave strong gradients in prevalence by risk group than country data, which showed relatively similar prevalences across groups, especially in PNG (Figure 2), where risk behaviours and STIs [40-45] are believed to be widespread, and sexual networks denser than elsewhere in South Asia or other regions, as evidenced also by a high degree of homology among HIV viral strains [46-49].

The third sensitivity analysis varied sexual mixing across the 7 groups, adding mixing between medium- and high-risk heterosexuals (which the default mixing matrix excluded; Annex 4b). Under this alternate mixing, the ranking of impacts across interventions was largely maintained, except that interventions targeting FSW – especially condoms – became more impactful notably in comparison to clinical treatment as a stand-alone intervention, which is not targeting these higher-risk contacts (Figure A4b).

As an alternative approximation of having a larger group of higher-risk men mixing with the low- and medium-risk population, we explored a calibration with larger population of higher-risk men, and smaller population of medium-risk men. The larger number of higher-risk men was compensated by a lower number of high-risk (FSW) contacts per man per year, such that baseline prevalence fit was maintained. This calibration resulted in broadly similar ranking of the interventions and intervention packages, compared to the default (Annex 4c). Due to the larger high-risk male (FSW client) population, relative impact increased slightly for interventions and packages targeting FSW (condoms and screening) while it decreased for less FSW-targeted interventions, viz. clinical treatment of symptomatic primary/secondary cases across all groups, and the 'medium' package with moderate coverages of all interventions.

A final, fourth sensitivity analysis examined how the default mixing structure may over-estimate risk and prevalence in low-risk heterosexual groups, resulting from the model's compartmental structure by which low-risk individuals effectively have a different (marital) partner annually. In a stand-alone simulation (Annex 4d), risk and resulting prevalence to low-risk people was simulated on an individual basis, in the extreme case of having one unique partner throughout the simulation. This simulation gave 0.83-fold to 0.85-fold lower prevalence, compared to the default model, within a range of initial low-risk prevalence of 0.05-3.0%. This illustrates that our compartmental model, by ignoring the real pair-based risk structure for low-risk people, slightly over-estimates country-level incidence (calculation in Annex 4d) – a minor bias that is unlikely to affect patterns of intervention effectiveness.

DISCUSSION

Results from the SITE model highlight several well-established but often neglected principles to syphilis control planning – for both high-burden (PNG) and moderate-burden (Peru) settings. Among biomedical interventions, those targeting the early, infectious stage (symptom-driven clinical treatment, and contact tracing) are the most impactful and cost-effective for eliminating adult transmission. Naturally,

behavioural risk reduction, through higher condom usage or reduced partner change rates also reduce transmission.

The extent to which behavioural interventions and clinic-based treatments can be successfully implemented in programmatic practice remains uncertain. Such interventions have been available and tried for decades, with varying success and epidemic resurgence in many settings [2, 39, 50]. High clinical treatment coverage requires people to recognize their symptoms, seek and receive treatment timely. Improved symptom recognition and timely treatment seeking are challenging goals for STI programs, and their levels and determinants are not well known. With lower than the assumed 60% of primary/secondary episodes symptomatic, the impact and cost-effectiveness of clinical treatment (but not contact tracing) would be at least proportionally lower than in the scenarios presented (sensitivity analysis not shown).

Screening is effective and cost-effective mainly if targeting high-risk groups (FSW, and secondarily MSM) and if carried out at least annually [23, 51, 52]. The SITE model may however over-estimate screening effectiveness and its contribution to elimination, as it assumed equal, random coverage of all individuals within a group. In reality, some people may systematically be missed by screening.

Unlike most syphilis models [19, 20, 24, 25, 27, 28], SITE explicitly relates successive stages of infection to distinct outcomes on (varying) test algorithms used in screening and surveillance. The 7-groups structure, matching the design of typical national STI data collection and target setting, facilitates use by national STI program staff to inform and optimize intervention packages. As with Spectrum-Goals, used by many national HIV/STI programs, this syphilis program planning tool should be teachable within a few days and become equally popular.

As for any model, the validity and accuracy of projections is limited by uncertainties in parameters and model structure. Sensitivity analyses varying rates of incidental cure revealed that for a given model fit to prevalence data, underlying infection incidence (for which no calibration data exist) and the consequent overall feasibility of elimination, can vary considerably.

Of note, the modelled ratio between prevalence and incidence, and indication of average duration of infection (weighted between treated and untreated episodes), was around 6.2 years in Peru and 7 years in PNG. For both countries, this is longer than the 2016 WHO regional STI estimates for Latin America and Oceania, of 2.4 and 4.1 years, respectively. Since also the SITE prevalence estimates were below WHO's, the resulting incidence estimates were far below WHO's latest regional estimates. These systematic differences may reflect one or more factors:

- SITE projections under-estimated effective treatment coverage (through clinical services and screening coverage combined) and/or the coverage of accidental cure;
- Peru and PNG have worse treatment coverage than other countries within their regions;
- treatment coverage worsened since the time that WHO estimation assumptions were set, which could have contributed to higher incidence (and outbreaks) in some populations.

As additional limitations, we note:

- The model represented FSW and MSM each as homogeneous group, with STI exposure and access to screening and treatment distributed equally. In reality, these groups feature – sometimes strong – gradients of risk and service uptake, and some subgroups are systematically un-reachable (and thereby even not identified as part of the high-risk group). More heterogeneity and more widespread risk tends to make elimination more difficult, a feature that the SITE model captured rather in terms of the varying mixing structures (members of any risk group may be heterosexually married to low-

risk individuals; sensitivity analysis added mixing between medium-risk and high-risk groups) – and earlier models in the form of sub-groups of FSW [23].
- The model ignored age patterns. Although available population-based surveys do not point to consistent age variations in adult syphilis (e.g. [53, 54]), age is a relevant intervention targeting criterion, e.g. screening adolescents.
- Cost-effectiveness analyses could be refined with country-specific, current unit costs; the current cost-related results are mainly indicative of the model's functionality.
- The two countries' epidemic calibrations were based on data extracted from literature publicly available up to 2019, without input from country HIV/STI program experts; intervention scenarios were generic examples not adapted to the respective local program contexts. Since then, country-tailored scenario development with the national STI/HIV programs have started with both countries.

Finally, the uncertainties in natural history parameters, and these unknowns and country variations in sexual network structure compound each other. We have not pursued formal multivariate uncertainty analysis, but rather did sensitivity analysis on key parameters and structural features. Overall, we qualify our results as indicating broad patterns, which should be valid especially in terms of rankings across interventions – but not precise quantifications or predictions.

Of note, our analyses compared cost-effectiveness within syphilis elimination strategies. In addition to adult infections, the presented strategies will avert cases and deaths from tertiary syphilis, and congenital syphilis. Averting congenital syphilis through screening of ANC women, although less effective for epidemic elimination, is cost-effective by itself [55]. For a valid comparison with other disease and health programs, such secondary benefits would have to be included, for example in composite measures like disability-adjusted life years lost.

In conclusion, the SITE model provides a user-friendly tool for STI planners to explore and prioritize impactful and cost-effective program pathways. Despite some inherent uncertainties in the natural history and transmission of syphilis, the projections highlight the power and necessity of symptom-based treatment of early syphilis, amplified by contact tracing. As more programs will intensify syphilis control and its monitoring and evaluation, the model structure and assumptions could be validated and refined, incrementally strengthening insights and lessons to roll-out and replicate success and progress towards a syphilis-free world.

Table 1. Baseline parameter values

(a) Global natural history parameters

Parameter (compartment in Figure 1)	**Symbol in equations**	**Value & unit**	**Uncertainty range**	**Source & comments**
Duration of infection:				South Africa model [19] and WHO global estimates [7, 29, 30]
Incubation (1)	$1/\sigma 1$	4 weeks	2-6	
Primary + secondary stage, untreated (2)	$1/\sigma 2$	28 weeks	18-78	Longer than the commonly assumed 18-26 weeks [19-21, 24, 25, 27, 28], as the SITE model does not explicitly distinguish symptomatic, infectious recurrences from Latent stage; these are instead incorporated within Compartment 2
Latent (3), untreated but considering an average rate of incidental cure, from antibiotic exposure to other infections	$1/\sigma 3$	780 weeks	260-1,560	Incidental cure, from exposure to oral penicillin, tetracyclines like doxycyclin, macrolides like azithromycin or other antibiotics taken for skin, respiratory and other non-STI-infections [56, 57] is believed to be common. In Brazil, prior to national legislation and regulation in 2011 and 2015 limited antibiotic use without medical prescription, penicillin and other antibiotics effective against syphilis were commonly used for sore throat, respiratory illness, and urinary tract infections, including through auto-medication by lay persons [58]. Globally, over 740 million dosages of azithromycin were used in mass campaigns against trachoma in trachoma-endemic countries since 1999 [59]. We assumed latent syphilis, when not detected and treated following programmatic screening, to last 15 years, as in WHO global STI estimates [7, 29, 30]. This is above the 10 years in South Africa's model [19], since in the SITE model, durations additionally get shortened by programmatic screening, which South Africa's model did not explicitly consider
Recovered after treatment (4)	$1/\sigma 4$	26 weeks	3-260	[19]
Incidentally cured (5)	$1/\sigma 5$	130 weeks	3-260	[19]
Susceptible to reinfection (6)	λ	Dynamic result		[19] Force of infection: see Annex 1
Treatment of Primary/secondary cases:				

Parameter (compartment in Figure 1)	**Symbol in equations**	**Value & unit**	**Uncertainty range**	**Source & comments**
Primary/Secondary cases that are symptomatic	ρ	60%	40-85%	[7, 19, 29, 30]
Probability of cure when treated, after clinic attendance for symptoms of Primary/Secondary infection	ψ	90%	54%-95%	54-93.4% in Peru [60, 61] and South Africa [19]; 95% (or lower for late latent cases) in HIV-infected patients treated with oral amoxicillin plus probenecid [62]; 61% estimated for Uganda [63]. Evidence is mixed as to whether effectiveness may be less for latent syphilis when treated with only a single dose of penicillin, as may be common in blanket screening programs – whereas for latent syphilis three dosages of penicillin are recommended [64, 65]. The 90% is conservative, to account for (1) lower effectiveness of single-dose treatments against latent syphilis, and (2) a 'yo-yo' effect of people getting re-infected soon by their (stable) partners, in the absence of contact referral
Primary + Secondary stage cases who upon treatment turn RPR-seronegative immediately	ϕ	40%		[19]
Transmission probabilities per sexual act:				
Man-to-woman		0.08	0.0008-0.30	[19, 26, 66, 67], applying during Primary + Secondary stage only
Woman-to-man		0.04	0.0005-0.20	[19, 26, 66, 67], applying during Primary + Secondary stage only
MSM		0.10	0.001-0.10	[24-27, 51], applying during Primary + Secondary stage only
Reduction in transmission probability, per act, from condom usage		80%	80-90%	[26, 68-72]. The model distributes usage randomly over all relationships and contacts (within each combination/pair of risk groups). In reality, usage is somewhat consistent and hence more effective; however higher condom efficacy, at condom rates as reported in surveys would result in unrealistically large syphilis declines

(B) Country-specific parameters

Population group	**PNG**		**Peru**		**Source & comments**
	1985	**2018**	**1985**	**2018**	
Clinical treatment of symptomatic Primary/ Secondary episodes (υ1)					
Low-risk Women	25%		25%		

Population group	PNG		Peru		Source & comments
	1985	2018	1985	2018	
Medium-risk Women	25%		25%		Peru: 5% medical treatment of all active/recent syphilis; 28.6-50% of females/males/MSM used medicine for self-reported GUD [73]. PNG: Values corresponding to WHO's 'Low treatment access' group of countries [7, 30].
High-risk Women = FSW	35%		**50%**		
Low-risk Men	35%		**50%**		
Medium-risk Men	35%		**50%**		
High-Risk Men = FSW clients	35%		**60%**		
MSM	35%		**60%**		
Contact tracing rate (ç)					
All groups	0%		0%		
Screening coverage, per year (α)					
ANC women		**20%**		**70%**	PNG: based on 2017 ANC-1 coverage (54% [74], ANC-based syphilis screening (44%) and syphilis treatment with penicillin (81%) [34]. Peru: 96.9% ANC-1 (2014 Demographic and Health Survey (DHS), [75]), 94% screening and 94% treatment coverage in 2017 [76]
Low-risk Women	0%	**10%**	0%	**24%**	
Medium-risk Women	0%	**10%**	0%	**24%**	
High-risk women = FSW	25%	35%	15%	40%	MSM & FSW: Considering counseling/outreach coverage assumed in global Fast Track projections; PNG 2018 program results [34]; service targets of PNG's 2018-2022 national HIV/STI strategy [74]
Low-risk Men	0%	0%	0%	0%	
Medium-risk Men	5%	5%	5%	5%	
High-risk Men = FSW clients	15%	15%	15%	15%	
MSM	15%	35%	15%	15%	
Population size (of all women or all men, 15-49 years)					
FSW, of women	1.6%		**0.9%**		PNG: national size estimations [35, 77, 78]; Peru: national estimates using Spectrum/Epidemic Projection Package estimates for HIV (http://aidsinfo.unaids.org/)
High-risk/FSW clients, of men	16.0%		**9.0%**		Fitting parameter, matched and balanced with FSW group size and numbers of FSW-client contacts, and considering behaviours reported in DHS [75, 79, 80]
MSM, of men	2.2%		**3.2%**		PNG: national size estimations [78, 81]; Peru: national Spectrum/Epidemic Projection Package estimates (http://aidsinfo.unaids.org/)
Medium-risk / with casual partners, of women or of men	30.5%		30.5%		Demographic and Health Surveys and other surveys

Population group	PNG		Peru		Source & comments
	1985	2018	1985	2018	
MSM that are married (bridging into the low-risk heterosexual population)	20%		25%		PNG: IBBS [35, 77]; Peru: [33, 82]
Condom use: sex acts protected					
Medium-risk	1%	15%	1%	15%	IBBS & DHS
High-risk (FSW/client)	1%	50%	**21%**	45%	
MSM	1%	63%	**27%**	50%	

Notes to Table 1: In panel 1B, bold values indicate those that drive the higher syphilis rates in PNG compared to Peru.
If no value is indicated for 2018, the value was the same as in 1985.

Table 2. Intervention coverages, by scenario

Scenario	Clinical treatment		Screening				Condoms (% of acts)			Comments
	Symptom-driven	Contacts traced per index	Low- & Medium-risk women	Low, Medium & High-risk men	FSW	MSM	FSW / client	MSM	FSW, MSM & medium-risk	
Constant coverage	*									
Treat 60% of symptomatics	60%[$]									As maximum feasible, based on the WHO global syphilis estimates for high-income, good treatment access countries of 85% [7, 29, 30]
Treat: 60% symptomatics + contacts	60%[$]	0.4								
Contact tracing		0.4								
Treat 50% of symptomatics	50%[$]									
Treat: 50% symptomatics + contact tracing	50%[$]	0.4								
Screen, FSW					80%					PNG's national HIV strategy targets 90% service coverage for FSW and MSM by 2022 [83]
Screen, MSM						80%				
Screen, Heterosexual men				20%						Low, Medium & High-risk groups
Screen, Low-risk + Medium-risk women			30%							
Condoms: FSW/client							75%			In comparison, UNAIDS Fast Track target [31] and PNG's National HIV strategy for 2022 target 90% use in FSW, MSM and medium-risk / casual contacts
Condoms: MSM								65%		
Condoms: FSW/client, medium-risk/casual & MSM							75%	65%	50%	
Elimination package	60%	0.4	30%	20%	80%	80%	75%	65%	50%	
Medium-term / realistic package	50%	0.2	20%	10%	60%	40%	60%	45%	30%	

Notes to Table 2: * Empty cells denote coverage, throughout 2019-2030, as in 2018.

[$] Some groups in Peru had baseline coverage already above 50% or 60% (Table 1b); in which case this 2018 coverage was maintained throughout 2030.

Table 3. Modelled distribution of national populations and prevalent and incident syphilis infections, adults 15-49 years, in 2018

A. PNG

Women:	Population	Prevalence, RPR+ TPHA+	Incidence / 1000 person-years	Incident cases	Share in incidence	Symptomatic cases treated	Persons screened	Screened, found positive
Not sexually active	14%	-	-	-	-	-	-	-
Low-risk	51%	0.81%	1.03	1,073	8%	135	106,228	883
Medium-risk (casual partnerships)	33%	4.2%	5.71	3,713	28%	467	68,201	2,914
High-risk = FSW	1.6%	7.0%	28.7	890	7%	151	11,821	821
All Women	**100%**	**1.9%**	**2.74**	**5,676**	**43%**	**753**	**186,250**	**4,618**
							186,250	4,618
Men:								
Not sexually active	14%	-	-	-	-	-	-	-
Low-risk	40%	0.77%	0.62	529	4%	92	-	-
Medium-risk (casual partnerships)	28%	4.1%	5.35	3,104	24%	533	30,387	1,248
High-risk = FSW clients	16%	2.7%	6.16	2,048	16%	335	52,042	1,429
MSM	2.2%	10%	41.9	1,769	13%	268	16,665	1,610
All Men	**100%**	**2.10%**	**3.44**	**7,449**	**57%**	**1,228**	**99,094**	**4,287**
All Women + Men		**2.01%**	**1.45**	**13,125**		**1,981**	**285,344**	**8,905**

B. Peru

Women:	Population	Prevalence, RPR+ TPHA+	Incidence /1000 person-years	Incident cases	Share in incidence	Symptomatic cases treated	Persons screened	Screened, found positive
Not sexually active	14%	-	-	-	-	-	-	-
Low-risk	52%	0.21%	0.47	1,999	8%	241	1,019,221	2,235
Medium-risk (casual partnerships)	33%	1.06%	2.12	5,787	24%	711	645,201	7,151
High-risk = FSW	0.9%	5.57%	24.39	1,627	7%	331	28,306	1,580
All Women	**100%**	**0.51%**	**1.14**	**9,414**	**39%**	**1,283**	**1,692,728**	**10,966**
				9,414		1,283	1,692,728	10,966
Men:								
Not sexually active	10%	-	-	-	-	-	-	-
Low-risk	50%	0.40%	0.26	1,096	5%	261	-	-
Medium-risk (casual partnerships)	28%	2.15%	2.04	4,776	20%	1,130	116,971	2,575
High-risk = FSW clients	9%	2.3%	5.27	3,859	16%	987	112,685	2,581
MSM	3.2%	8.0%	20.83	5,075	21%	1,115	40,191	3,193
All Men	**100%**	**1.27%**	**1.76**	**14,807**	**61%**	**3,493**	**269,847**	**8,349**
All Women + Men		**0.89%**	**1.45**	**24,221**		**4,776**	**1,962,576**	**19,314**

Table 4. Cost and cost-effectiveness of syphilis control and elimination scenarios

(a) PNG

Service delivery volumes, 2019-2030:	Screening		Treatments					Infections averted, 2019-2030	Cost per infection averted
	Screenings	Contacts traced	Index patient	Positives on screening	Contacts traced & diagnosed	Condoms distributed	Cost, 2019-2030		
Constant, at 2018 coverages	3,932,215	-	27,678	108,540	-	-	$ 8,681,185	-	
Screen, Low+Medium-risk F	8,722,261	-	22,864	138,457	-	-	$ 18,655,571	32,972,987	$ 0.57
Screen, FSW	4,139,903	-	24,164	103,616	-	-	$ 9,071,581	22,577,677	$ 0.40
Screen, Heterosexual men	7,807,569	-	23,474	139,304	-	-	$ 16,773,386	28,389,207	$ 0.59
Screen, MSM	4,225,630	-	24,803	103,065	-	-	$ 9,250,257	19,095,014	$ 0.48
Contact tracing (treatment as in 2018)	3,932,215	9,168	23,722	91,583	4,738	-	$ 8,640,629	26,565,716	$ 0.33
Treatment, 50% of symptomatics	3,932,215	-	22,429	80,500	-	-	$ 8,547,177	89,011,930	$ 0.10
Treatment 50% + Contact tracing	3,932,215	7,276	19,032	66,530	2,768	-	$ 8,506,155	103,593,184	$ 0.08
Treatment 60% of symptomatics	3,932,215	-	19,333	69,921	-	-	$ 8,490,187	116,333,997	$ 0.07
Treatment 60% + Contact tracing	3,932,215	6,324	16,516	57,602	2,090	-	$ 8,452,922	126,588,815	$ 0.07
Condoms, commercial	3,932,215	-	20,577	88,294	-	28,289,111	$ 12,808,704	47,252,254	$ 0.27
Condoms, MSM	3,932,215	-	24,736	95,996	-	6,534,785	$ 9,598,026	21,078,187	$ 0.46
Condoms, commercial & casual & MSM	3,932,215	-	6,566	57,699	-	287,200,582	$ 51,451,449	149,681,030	$ 0.34
Elimination package	13,098,717	1,846	5,204	86,279	453	287,200,582	$ 70,484,473	172,062,282	$ 0.41
Medium-term/Realistic package	7,849,199	2,863	12,512	86,619	953	118,936,949	$ 34,452,915	133,637,236	$ 0.26

(b) Peru

Service delivery volumes, 2019-2030:	Screening		Treatments		Contacts traced & diagnosed			Infections averted, 2019-2030	Cost per infection averted
	Screenings	Contacts traced	Index patient	Positives on screening		Condoms distributed	Cost, 2019-2030		
Constant, at 2018 coverages	24,911,559	-	54,606	196,426	-	-	$ 52,483,952	-	
Screen, Low+Medium-risk F	30,175,206	-	52,461	202,531	-	-	$ 63,363,601	12,209,195	$ 5.19
Screen, FSW	25,267,909	-	46,790	186,965	-	-	$ 53,139,750	35,654,542	$ 1.49
Screen, Heterosexual men	40,538,159	-	48,664	248,413	-	-	$ 84,910,974	31,412,590	$ 2.70
Screen, MSM	27,112,856	-	40,872	200,038	-	-	$ 56,963,817	65,982,024	$ 0.86
Contact tracing (treatment as in 2018)	24,911,559	19,466	46,385	162,748	7,692	-	$ 52,394,452	41,652,638	$ 1.26
Treatment, 50% of symptomatics	24,911,559	-	52,960	177,798	-	-	$ 52,405,538	44,363,807	$ 1.18
Treatment 50% + Contact tracing	24,911,559	18,820	45,239	147,817	6,815	-	$ 52,326,441	76,913,391	$ 0.68
Treatment 60% of symptomatics	24,911,559	-	46,061	155,101	-	-	$ 52,281,784	99,522,882	$ 0.53
Treatment 60% + Contact tracing	24,911,559	16,720	39,514	129,327	5,372	-	$ 52,212,752	123,363,259	$ 0.42
Condoms, commercial	24,911,559	-	37,830	160,132	-	73,275,962	$ 63,244,343	78,639,152	$ 0.80
Condoms, MSM	24,911,559	-	42,568	174,084	-	33,975,621	$ 57,428,227	60,972,918	$ 0.94
Condoms, commercial & casual & MSM	24,911,559	-	13,121	106,644	-	1,075,724,959	$ 213,271,336	217,897,862	$ 0.98
Elimination package	48,359,453	3,458	9,236	153,834	728	1,075,724,959	$ 261,854,591	247,434,387	$ 1.06
Medium-term/Realistic package	28,787,173	4,992	22,265	152,553	1,285	457,984,178	$ 128,853,320	180,262,343	$ 0.71

Notes to Table 4. Screening used RPR, with or without TPHA-based confirmation. In calculation of treatment volumes required for a given screening coverage, sensitivity and specificity of diagnostic tests was ignored, for the following reasons:

- Estimated sensitivity and specificity of syphilis tests are typically close to 100% [84], and will likely improve in next-generation tests to be adopted by elimination programs;
- Test sensitivities and specificities probably vary with risk and prevalence of groups being screened, but these variations have not been established systematically; so adjustments relevant for one population may not be appropriate for another. For example, in Port Moresby in PNG, of parturient women positive on the (Venereal

Disease Research Laboratory (VDRL) test 86% were TPHA positive [85], a higher proportion than a global average of 0.53 from meta-analysis [86].

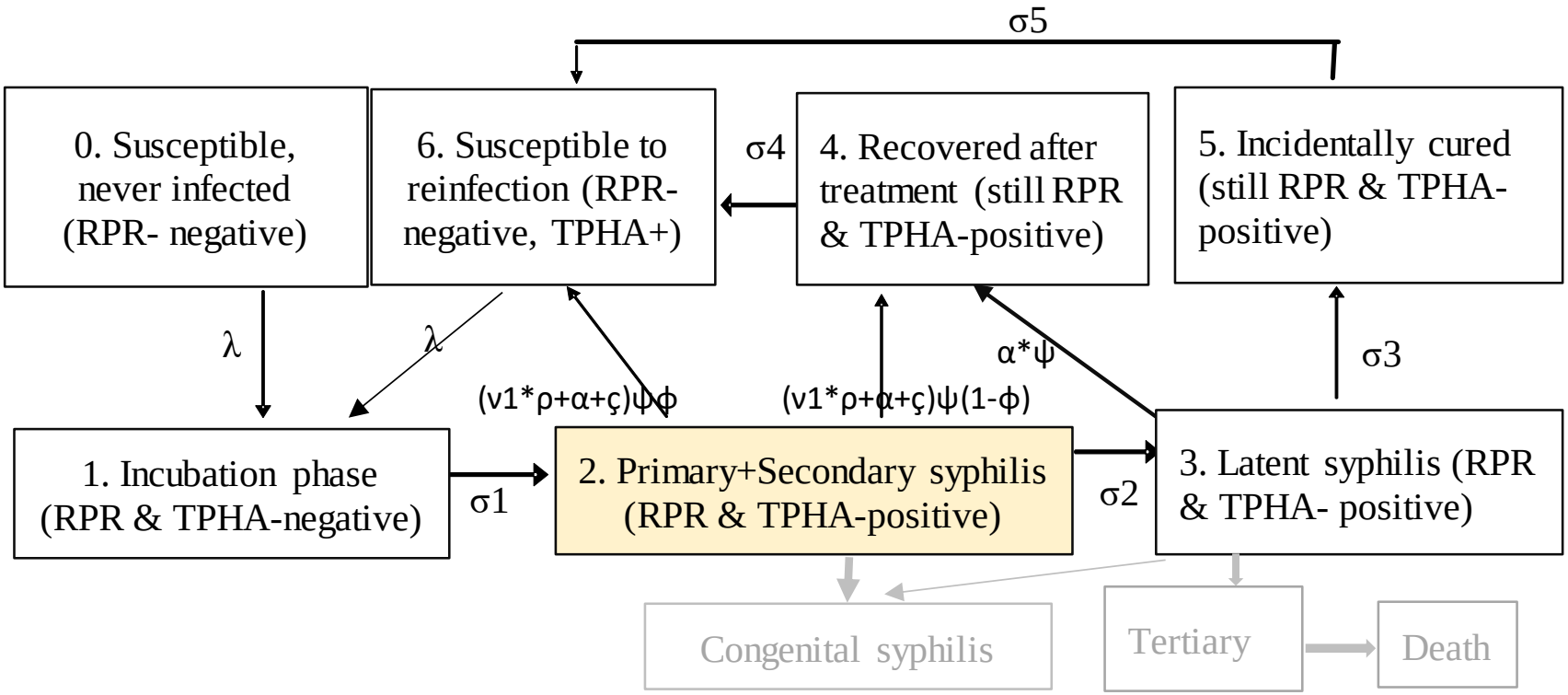
- In programmatic practice, a <100% specificity will result in some unnecessary treatments of people screening false-positive, but with the low syphilis treatment cost his is a negligible concern. If needed, model users could add a volume of additional treatments (resulting from a <100% test specificity) onto model outputs, to account for this;
- Ignoring sensitivity implies that for a given screening coverage, the transmission impact may be over-estimated – but users can adjust for this by capping maximum screening coverage below 100%, at the level of the sensitivity of the test or algorithm considered.

The most cost-effective interventions are shaded green.
Unit costs assumed for scenario costing and cost-effectiveness analysis:

- 1 adult screened (as average across possible screening algorithms: US$ 2.1, based on 2012 bulk procurement data reported to WHO also quoted in a global congenital syphilis investment case analysis [55].
- 1 adult with confirmed syphilis treated for syphilis (costing 3 doses of benzathine penicillin; labor and supplies & counseling): US$ 5.8, based on a global congenital syphilis investment case analysis, quoting 2012 bulk procurement data reported to WHO [55], built up of $ 3.7 for treatment + counselling & $ 2.1 for testing.
- 1 syphilis-adult contact-traced and treated: US$ 5.5, which includes the tracing activity but excludes the cost of testing contacts of index cases, which was costed at $ 2.1 per contact tested, applied to the volume of contacts shown in column ‘Contacts traced’.
- 1 condom distributed (including procurement, distribution and promotion/counselling): US$ 0.15, based on assumptions in the Global Fast Track HIV/AIDS costing [31], and similar to the Asia regional estimate of $ 0.14 in Avenir Health’ global unit cost repository [87].

Treatment costing was for etiological case management, as opposed to the syndromic approach, WHO-recommended and demonstrated impactful and cost-effective for settings with limited laboratory capacity and health system infrastructure [88-91]. Syndrome-based case management includes (over-)treating many genital ulcers presenting to clinics for syphilis, while most are caused by HSV-2 [92]. In compensation, costs of clinical testing are lower. This intervention variant can be assessed in SITE by dividing model-outputted syphilis treatment cost by the local etiological fraction of syphilis among all genital ulcers presenting to clinics, and removing test cost for clinical treatment of symptomatic cases.

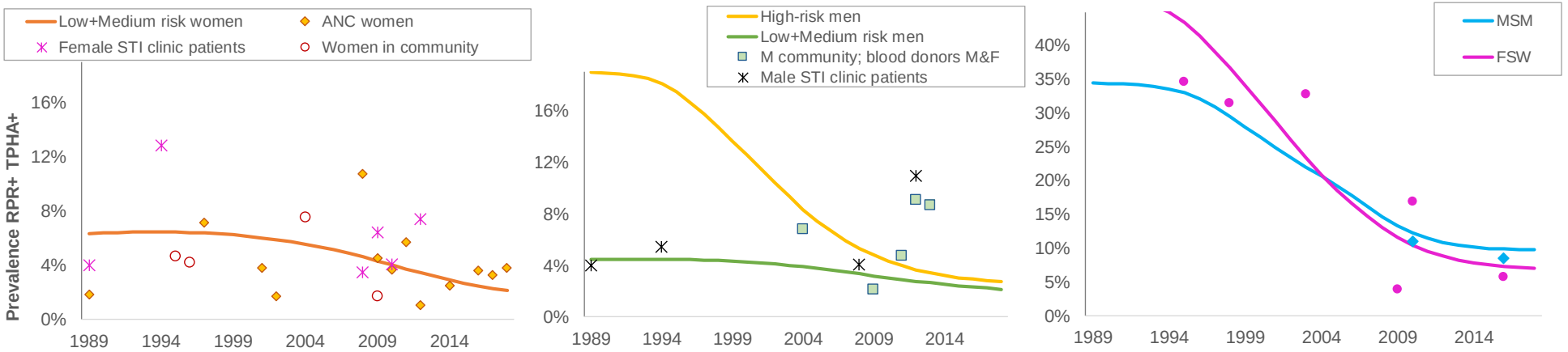
Figure 1. Syphilis natural history: flow between modelled infection stages i.e. compartments



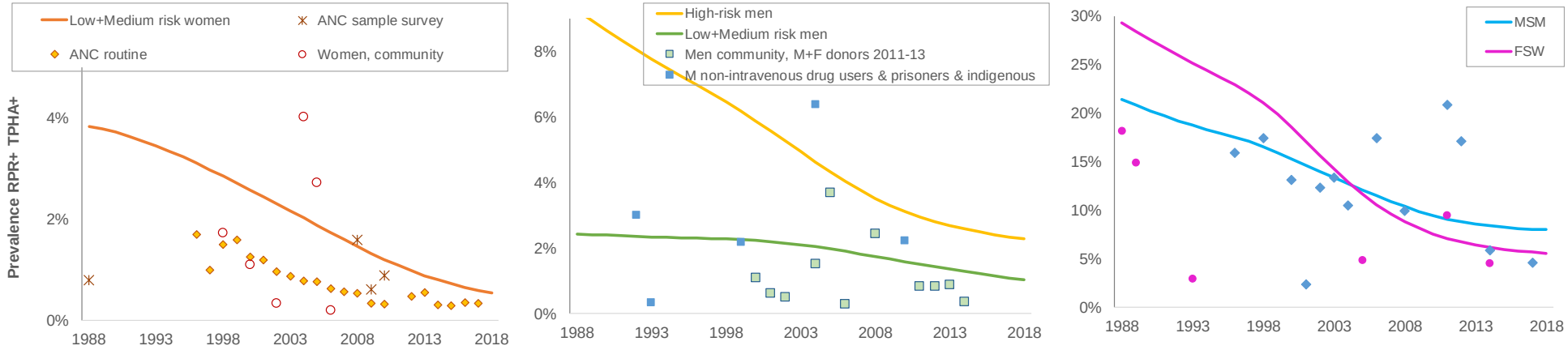
Notes to Figure 1: Parameter denotations, definitions and values are given in Table 1A.
Compartment 2 is shown in orange shade, as the one compartment that is infectious and driving transmission.
Outcomes Tertiary syphilis, Death from untreated syphilis and Congenital syphilis (in grey font) were not modelled, since these do not affect (i.e. transmit further into) the adult population, and population-based mortality data are scarce, requiring multi-year follow-up without treatment, which is unethical, cause of death certification, background mortality and small numbers [93]. These public health outcomes (including clinical variants of congenital syphilis: mis-carriages/still-births, Low Birth Weight / pre-term birth, and new-borns with clinical signs) can be calculated based on model-projected incidence and prevalence of Compartments 2 and 3, as a linear/proportional risk probability, using risk probabilities per pregnant infected mother as in [6].

Figure 2. Model fit to national syphilis prevalence data

a. PNG



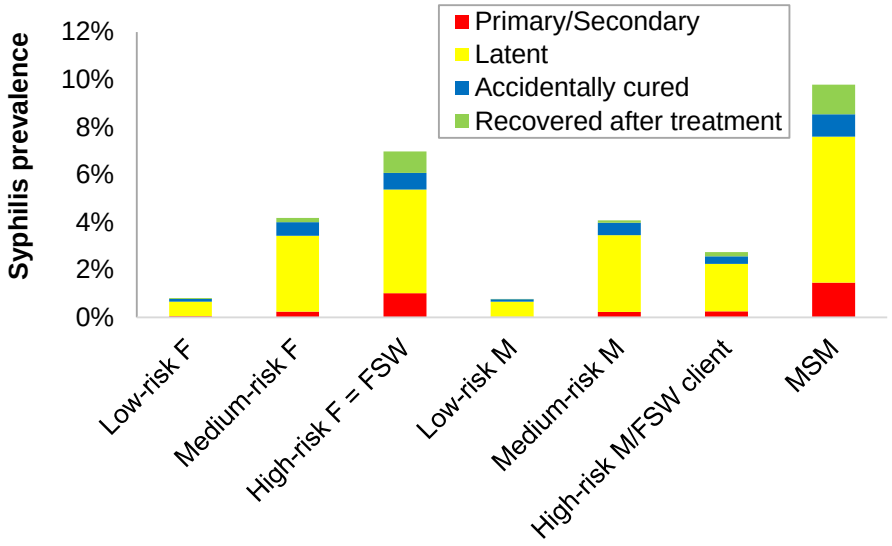
b. Peru



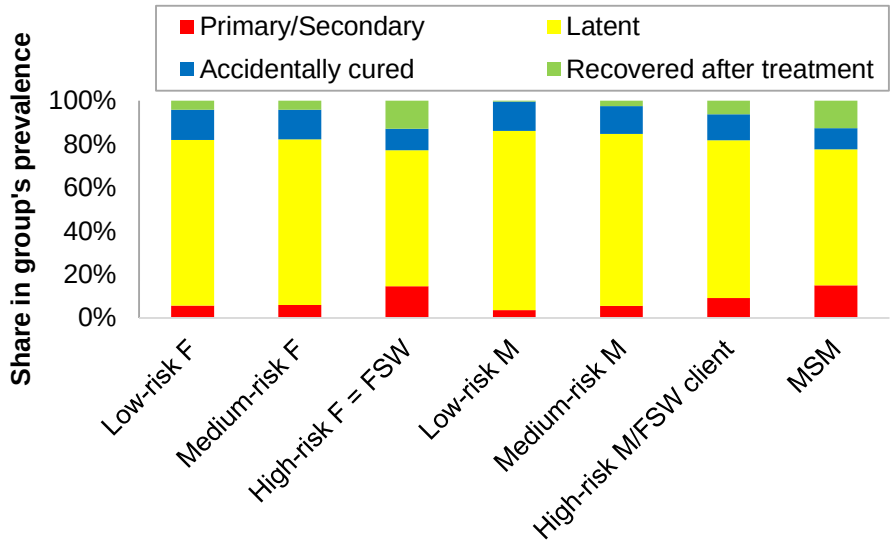
Notes to Figure 2. Neither country had data specific to low-risk versus medium-risk women or men; therefore in fitting prevalence to surveillance data, model outputs for low-risk and medium-risk women or men were combined. In the right-most panels, the lines are the model and dots are the data, both blue for MSM and pink for FSW.
The MSM data point shown for PNG in 2009 were male and transgender sex workers [94]; we use it as a proxy for MSM prevalence absent alternative MSM data. For PNG, not shown is a report of 20% prevalence in 2010, during a syphilis outbreak in an oil palm plantation estate (Hagita), with 20% of (male and female) workers sampled found infected [49]. For Peru, the modelled decline in MSM (solid blue line) is consistent with modelled trends in HIV incidence, driven by increasing condom usage [31, 33].
Prevalence calibration ignored cross-reactivity of RPR and TPHA with yaws, which is prevalent in PNG but tends to be differentially segregated geographically as well as by age (yaws in children, syphilis in adults) [95].

Figure 3. Modelled prevalence of syphilis, by stage and by risk group, 2018

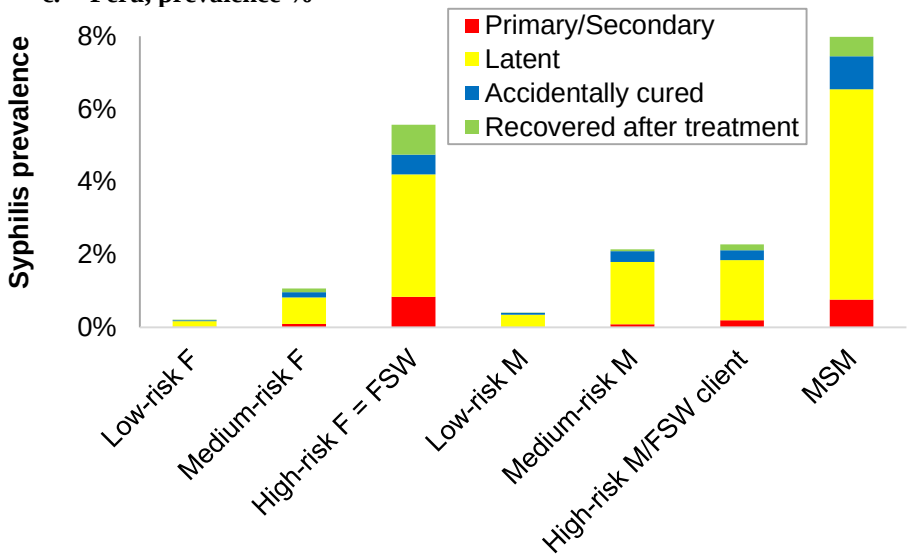
a. PNG, prevalence %



b. PNG, share of stage within a group's overall syphilis prevalence



c. Peru, prevalence %



d. Peru, share of stage within a group's overall syphilis prevalence

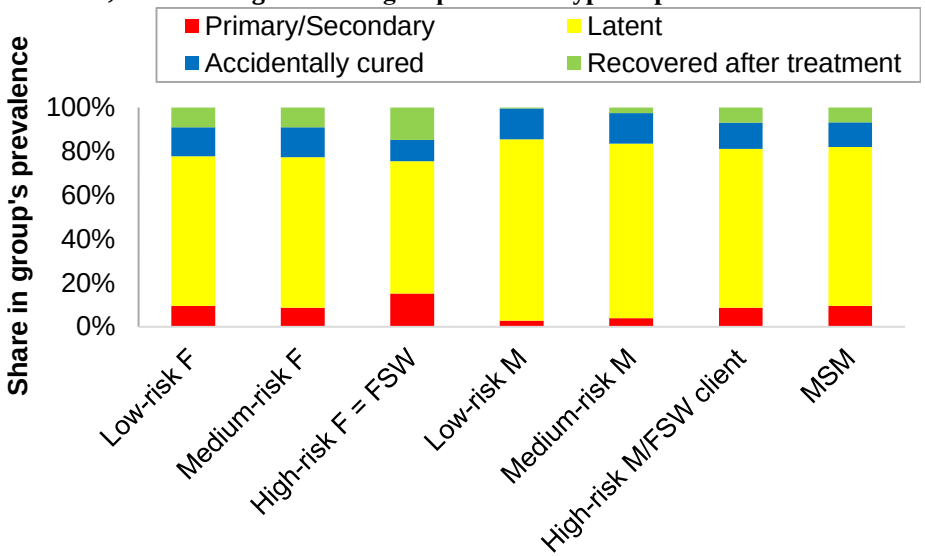
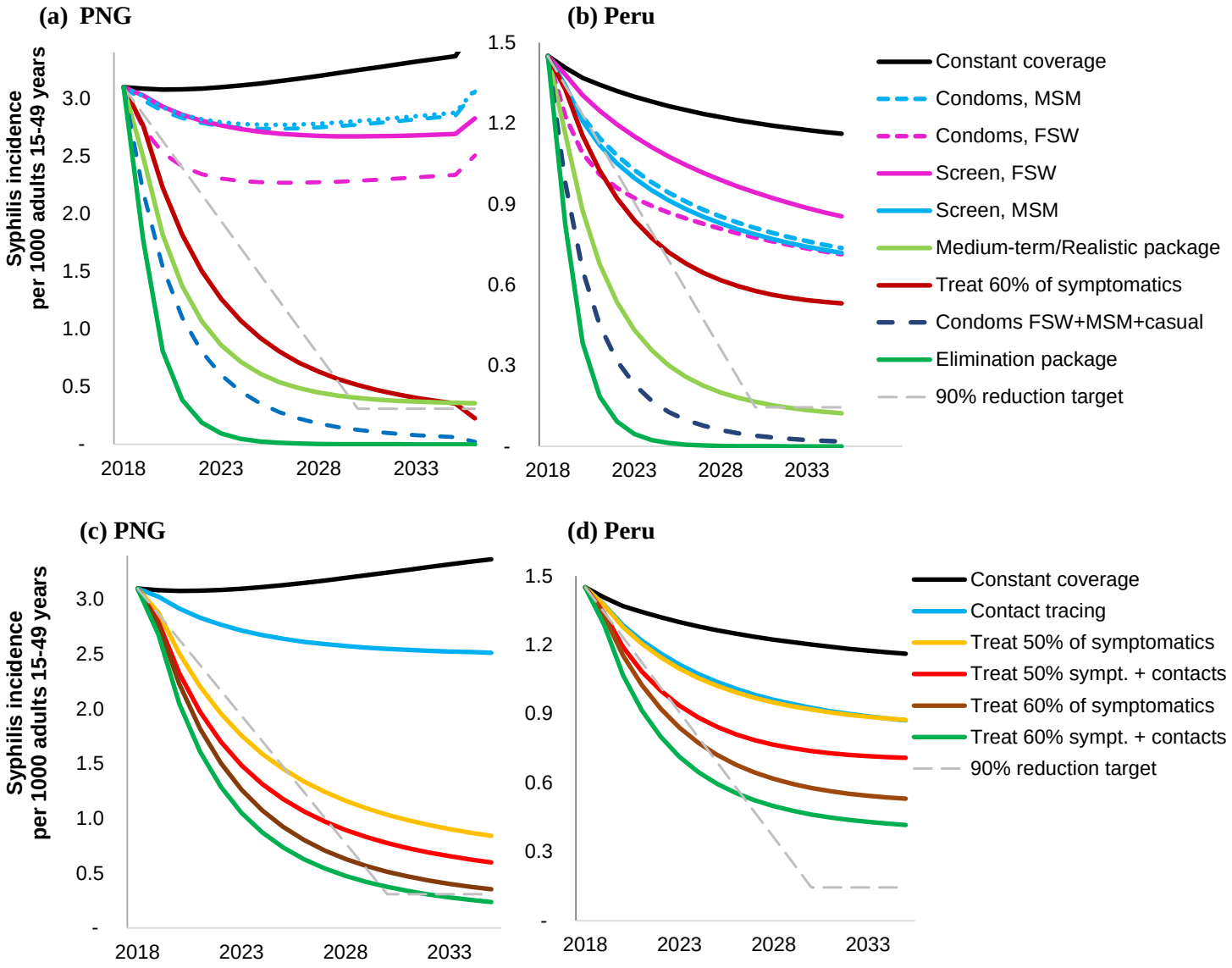


Figure 4. Syphilis incidence rate per 1000 adult person-years, in alternative prevention, screening and treatment scenarios:
(a) PNG; (b) Peru; (c) PNG, clinical treatment with versus without contact tracing;(d) PNG, clinical treatment with versus without contact tracing.



Notes to Figure 4, panels (c) and (d): Scaling-up clinical treatment to 50% or 60% of symptomatic Primary & Secondary episodes corresponds to the treatment coverage targets included in the Medium-term/Realistic and the Elimination scenarios described above, respectively. However this graph focuses on the effect of clinical treatment, with or without contact tracing (in all scenarios shown here, of around 0.40 contact per index), without combining with screening and/or behavioural / condom) interventions.

Annex 1. Model description

We consider the model presented in Figure 1. Let g and $r = 1 \ldots r_g$ denote the gender and risk group respectively; and let S_u^{gr}, S_i^{gr}, I^{gr}, P^{gr}, L^{gr}, R_e^{gr} and R_l^{gr} denote population in the groups: susceptible never infected (compartment 0), susceptible previously infected (Compartment 6), infected in incubation stage (Compartment 1), Primary or Secondary (Compartment 2), latent stage (Compartment 3), recovered after clinical symptom-based treatment or following syphilis screening (Compartment 4), and incidentally cured following antibiotic exposure for non-syphilitic conditions (Compartment 5), respectively.

The flow chart presented in Figure 1 can be translated mathematically using the system of ODEs:

$$\begin{cases} \frac{d}{dt}S_u^{gr}(t) = b_u^{gr}(t) - \lambda_{gr}(t)S_u^{gr}(t) - \mu S_u^{gr}(t) - \tau^{gr}S_u^{gr}(t) + \tau^{gr+1}S_u^{gr+1}(t) \\ \frac{d}{dt}S_i^{gr}(t) = \vartheta_1^{gr}(t)P^{gr}(t) + \frac{1}{\sigma_5}R_l^{gr}(t) + \frac{1}{\sigma_4}R_e^{gr}(t) - \lambda_{gr}(t)S_i^{gr}(t) - \mu S_i^{gr}(t) - \tau^{gr}S_i^{gr}(t) + \tau^{gr+1}S_i^{gr+1}(t) \\ \frac{d}{dt}I^{gr}(t) = \lambda_{gr}(t)S_u^{gr}(t) + \lambda_{gr}(t)S_i^{gr}(t) - \frac{1}{\sigma_1}I^{gr}(t) - \mu I^{gr}(t) - \tau^{gr}I^{gr}(t) + \tau^{gr+1}I^{gr+1}(t) \\ \frac{d}{dt}P^{gr}(t) = \frac{1}{\sigma_1}I^{gr}(t) - \vartheta_1^{gr}(t)P^{gr}(t) - \vartheta_2^{gr}P^{gr}(t) - \frac{1}{\sigma_2}I^{gr}(t) - \mu P^{gr}(t) - \tau^{gr}P^{gr}(t) + \tau^{gr+1}P^{gr+1}(t) \\ \frac{d}{dt}L^{gr}(t) = \frac{1}{\sigma_2}I^{gr}(t) - \vartheta_3^{gr}(t)L^{gr}(t) - \frac{1}{\sigma_3}L^{gr}(t) - \mu L^{gr}(t) - \tau^{gr}L^{gr}(t) + \tau^{gr+1}L^{gr+1}(t) \\ \frac{d}{dt}R_l^{gr}(t) = \frac{1}{\sigma_3}L^{gr}(t) - \frac{1}{\sigma_5}R_l^{gr}(t) - \mu R_l^{gr}(t) - \tau^{gr}R_l^{gr}(t) + \tau^{gr+1}R_l^{gr+1}(t) \\ \frac{d}{dt}R_e^{gr}(t) = \vartheta_2^{gr}(t)P^{gr}(t) + \vartheta_3^{gr}L^{gr}(t) - \frac{1}{\sigma_4}R_e^{gr}(t) - \mu R_e^{gr}(t) - \tau^{gr}R_e^{gr}(t) + \tau^{gr+1}R_e^{gr+1}(t) \end{cases}$$

where $b_u^{gr}(t)$ is the number of individuals entering the adult population; ϑ_1^{gr} and ϑ_2^{gr} are the rates at which individuals in primary and secondary stage are treated and become susceptible immediately after treatment, or recover but temporarily remain RPR+ and non-susceptible to re-infection ϑ_3^{gr} is the rate at which individuals in the latent stage are moved to the recovered after treatment, and satisfy $\vartheta_1^{gr}(t) = \left(\nu_1 + \alpha^{gr}(t) + c^{gr}(t)\right)\psi\phi$, $\vartheta_2^{gr}(t) = \left(\nu_1 + \alpha^{gr}(t) + c^{gr}(t)\right)\psi(1-\phi)$, $\vartheta_3^{gr}(t) = \alpha^{gr}(t)\psi$, $\nu_1$is the rate of treatment seeking during primary and secondary syphilis, α^{gr} is the screening rate, c^{gr} is the contact tracing rate (see below), ψ is the probability of cure when treated, and ϕ is the proportion of cases in primary and secondary stage that become RPR sero-negative immediately after treatment; λ_{gr} is the force of infection, μ is the rate at which individuals exit the sexually active population, $\tau^{gr}$is the turnover rate which was set to zero for all risk groups but Female Sex Workers, who are assumed to join the Medium-risk group after ending sex work, and $S_u^{gr} = S_i^{gr} = R_e^{gr} = R_l^{gr} = I^{gr} = P^{gr} = L^{gr} = 0$ if $r > r_g$.

Force of Infection: Coefficient/marriage structure/survey-data driven approach

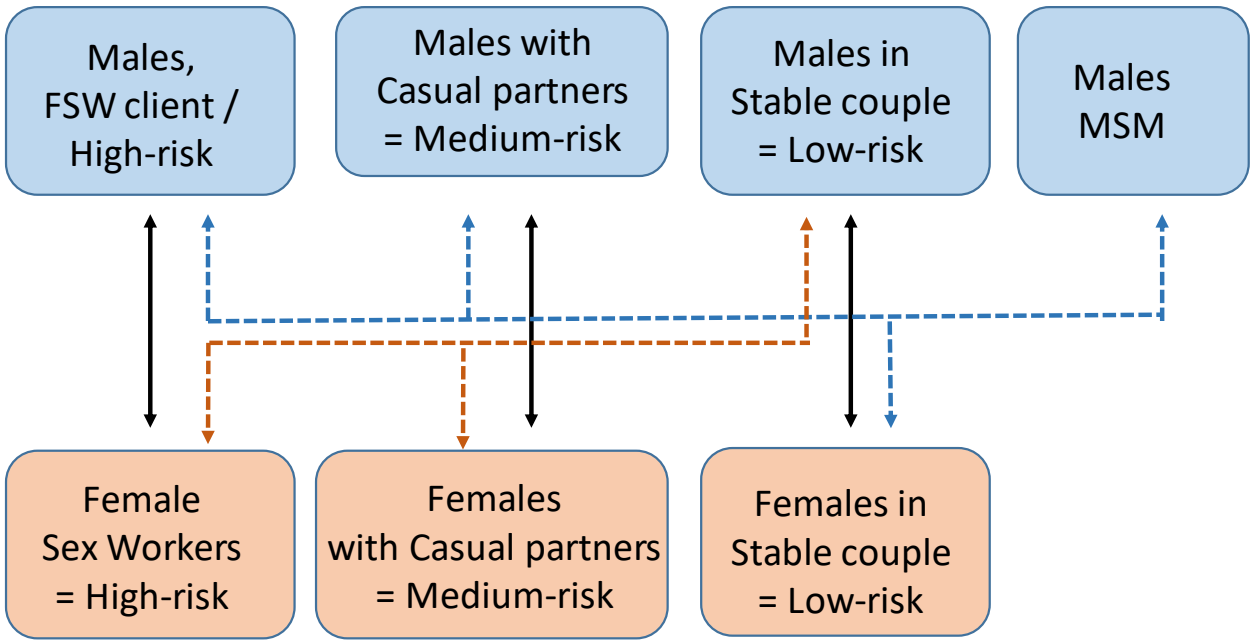
Transmission of infection in the syphilis model (default version) is calculated assuming balanced sexual mixing based on work by Garnett and Anderson [96, 97]. In this formulation, the population is stratified by sex $g \in \{F, M\}$ and behavioral risk r (1, low-risk heterosexual; 2, medium-risk heterosexual; 3: high-risk heterosexual; 4: men who have sex with men (MSM)). Sexual mixing preferences are expressed via coefficients $\tilde{q}_{g,r,g^*,j}(t)$ that quantify the nominal proportion of partnerships that group (g,r) prefers to draw from group (g^*,j) at time t. These satisfy $\tilde{q}_{g,r,g^*,j}(t) \geq 0$ and for any group (g,r), $\sum_{g^*,j}\tilde{q}_{g,r,g^*,j}(t) = 1$. These are "nominal" mixing because, in practice, sexual mixing depends on the supply and demand for partnerships. Each group (g,r) has size $N_{g,r}(t)$ and acquires new partners at rate $z_{g,r}(t)$. Balanced mixing requires that for all groups (g,r) and (g^*,j),

$$z_{g,r}(t)\tilde{q}_{g,r,g^*,j}(t)\Delta_{g,r,g^*,j}(t)N_{g,r}(t) = z_{g^*,j}(t)\tilde{q}_{g^*,j,g,r}(t)\Delta_{g^*,j,g,r}(t)N_{g^*,j}(t) \quad (1)$$

Actual levels of mixing are the product of the nominal coefficients $\tilde{q}_{g,r,g^*,j}(t)$ and balancing terms $\Delta_{g,r,g^*,j}(t)$ that adjust for imbalances in partnership supply and demand between groups. We define balancing terms as

$$\Delta_{g,r,g^*,j}(t) = \sqrt{\frac{z_{g^*,j}(t)\tilde{q}_{g^*,j,g,r}(t)N_{g^*,j}(t)}{z_{g,r}(t)\tilde{q}_{g,r,g^*,j}(t)N_{g,r}(t)}} \quad (2)$$

Figure A1. Risk group structure and mixing in the syphilis transmission model



Note to Figure A1. Black arrows indicate sexual relationships assorted by risk category; blue dashed arrows stable/marital relationships held by low-risk women with non-low-risk men: red dashed arrows stable/marital relationships held by low-risk men with non-low-risk women.

The force of infection $\lambda_{g,r}$ in the default model version is calculated based on the mixing between groups shown in Figure A1,

$$\lambda_{gr}(t) = \sum_{g^*}\sum_j m_{gr,g^*j}(t)\theta_{gr,g^*j}(t) \quad (3)$$

where m_{gr,g^*j} is the rate at which individuals of gender g and risk group r initiate partnerships with partners of sex g^* and in the risk group j, and $\theta_{gr,g^*j}(t)$ is the per-partnership transmission probability from an infected partner of sex g^* and risk group j to a susceptible sex g and in the risk group r.

We assume that "low-risk" individuals are those in one exclusive marital partnerships and individuals can be in marital partnerships (with the opposite sex), independently of their number of partners. We further assumed that only marital partnerships can be made of individuals of different risk groups (e.g. high-risk men only form partnerships with high-risk women (FSW) and/or low-risk women; MSM only form partnerships with MSM and/or low-risk women).

Let $q_{gr}(t)$ be the proportion of married (with the opposite sex) people of sex g and in risk group r. By assumption, all marital partnerships are monogamous and $q_{g1}(t) = 1$, i.e. all individuals in the low-risk group (r =1) are married (or cohabitating with one partner). Of note, marital relationships are modelled with annual remixing across all low-risk partners – i.e. they are slightly higher-risk than long-term monogamous relationships.

We determine the proportion of marriages between low-risk individuals and individuals in each respective risk group of the opposite sex using:

$$\tilde{q}_{g1,g^*r}(t) = \frac{q_{g^*r}(t)N_{g^*r}(t)}{\sum_j q_{g^*j}(t)N_{g^*j}(t)} \quad (4)$$

where $N_{g^*r}(t)$ is the number of individuals with sex g^* in the risk group r.

Derivation of Equation (4) can be found in [97, 98] and a discussion of the formula in [99]. There are alternatives to Equation (4), discussed in [28] and [97].

The actual propensity to engage in a marital partnership among individuals not in the low-risk group, $r > 1$, is given by:

$$\tilde{q}_{gr,g^*1}(t) = \frac{q_{gr}(t)}{z_{gr}(t)} \quad (5)$$

where $z_{gr}(t)$ is the reported mean number of partners per year of individuals of sex g and in risk group r, while the propensity of engaging in partnership with individuals with the same level of risk is:

$$\tilde{q}_{gr,g^*r}(t) = 1 - q_{gr}(t) + \ q_{gr}\frac{z_{gr}(t)-1}{z_{gr}(t)} \quad (6)$$

Then

$$m_{gr,g^*j}(t) = z_{gr}\tilde{q}_{gr,g^*j}(t)\Delta_{g,r,g^*,j}(t) \quad (7)$$

where $\tilde{q}_{gr,g^*j}$ is given by Equations (4) to (6)**Error! Reference source not found.**.

The per-partnership transmission probability was obtained using

$$\theta_{gr,g^*j}(t) = \pi_{g^*j}(t) - \pi_{g^*j}(t)\left(1 - \tau_{gr,g^*j}(t)\right)^{a_{gr,g^*j}(t)} \quad (8)$$

where $\pi_{g^*j}(t)$ is the proportion of infectious individuals of sex g^* in the risk group j, $a_{gr,g^*j}(t)$ is the number of sex acts that individuals of gender g and in risk group r have with individuals of sex $g^*$and in risk group j which, by assumption, equals the number of sex acts in marital partnerships if the partners are married; $\tau_{gr,g^*j}(t)$ is the probability that an infectious individual of sex g^* in risk group j transmits the infection to a susceptible individual of sex g in the risk group r, given by:

$$\tau_{gr,g^*j}(t) = (1 - e\kappa_{gr,g^*j})\tau_{g,g^*} \quad (9)$$

where $\tau_{s,s^*}$is the per-sex-act transmission probability from sex g^* to sex g, e is the efficacy of condom and $\kappa_{gr,g^*j} = 0.5(\kappa_{gr} + \kappa_{g^*j})$, if $r \neq 1$ and $j \neq 1$, $\kappa_{gr,g^*j} = 0.5(\kappa_{g1} + \kappa_{g^*1})$, if $r = 1$ or $j = 1$; $\kappa_{gk}$is the reported condom use in sex g and risk group .

In the mixing matrix FSW have a career duration specified by the user (in Goals calibrations for HIV epidemics in many countries, and in the syphilis calibrations here for PNG and Peru, typically set at 8 years), after which these women move to the medium-risk category.

This Force-of-Infection mechanism, and the sexual mixing matrix it interacts with, were designed with the Spectrum Goals model for HIV [16] as starting point. The syphilis model differs from Goals in that:

- Goals (for simplicity) assumes that low-risk women cannot infect medium-risk or high-risk men, and low-risk men cannot infect medium-or high-risk women. In the syphilis model, considering the much higher per-act transmission probability for syphilis than for HIV, this simplification was not made.
- Goals has additional risk groups of male and female IDUs.
- Goals has the option to stratify the MSM group into (up to 4) subgroups of lower-risk MSM and higher-risk MSM.

Annex 2. Contact tracing intervention

Contact referral is screening and treatment of partners of patients diagnosed following symptom-driven clinical treatment during Primary/Secondary stage syphilis. Coverage is specified as a proportion of Primary/Secondary stage index cases offered contact tracing, which multiplies with a proportion of his/her contacts who then get traced – separately for index cases in each of the 7 transmission groups, by calendar year.

Tracing results in treatment if the contact is also in the Primary/Secondary or Latent stage. Contacts traced are assumed to come from the sexual partner groups according to the sexual mixing matrix, except that FSW and their clients do not refer each other.

Prevalence i.e. yield among contacts is calculated dynamically, considering the following determinants.

- the duration of Primary/Secondary stage infection until treatment in the index case (e.g. 14 weeks, which is half the average duration of this stage if untreated);
- the chance that a contact infected by the index will still be in incubation stage, depending on user-specified lag from index case treatment to contact traced and diagnosed (e.g. 2 weeks, half of the average duration of incubation);
- the frequency of sex acts and per-act transmission probability;
- the chance that in some partnerships where contact tracing occurs, the contact trace may have been the first infected (before the index) instead of after/by the index (e.g. 50%), although this direction of transmission is unlikely:
    - First, the index would probably know of his or her partner's previous treatment and so not refer that contact;
    - Second, given that the index is more likely the first person infected in the partnership, there is little chance that the later infected partner would have been treated sooner than the index case;
- The background prevalence in the group from which a given contact comes.

So as to allow the user to fit program data about contact tracing yield, the input file has a composite parameter ε, ranging from 0 to 1, which indicates the success of index patients treated during in Primary/Secondary in identifying potentially infected partners. $\varepsilon = 1$ if index patients perfectly identify infected partners (identification post-infection) and $\varepsilon = 0$ if instead they refer in the contact tracing any of their partners completely at random.

Mathematically, this is implemented as follows:
More specifically, let $p_{gr}(t)$ be the proportion of individuals with symptomatic Primary/secondary syphilis and seeking treatment at time t. The number of contacts traced following diagnosis of these index cases is:

$$nc_{gr}(t) = p_{gr}(t) \sum_{g^*} \sum_j m_{gr,g^*j}(t) \chi_{gr,g^*j} N_{gr}(t) \quad (10)$$

where j represents the risk group of the partners, $m_{gr,g^*j}(t)$ is the mixing term, $\chi_{gr,g^*j}$is the probability that individuals in the index group refer their partners in group j to clinics, and $N_{gr}(t)$ is the number of individuals with sex g and in the risk group r.

The number of contacts traced who are in disease stage d (nc_{grd}) can be obtained by:

$$\mathrm{nc_{grd}(t)} = \mathrm{p_{gr}(t)} \sum_{g^*} \sum_{\mathrm{j}} \mathrm{m_{gr,g^*j}(t)} \chi_{\mathrm{gr,g^*j}} \tilde{\mathrm{p}}_{\mathrm{g^*j}}(\mathrm{t}) \mathrm{N_{gr}(t)} \quad (11)$$

where $\tilde{p}_{g^*j}(t)$ is the proportion of individuals in syphilis stage d, (d=0 for uninfected individuals, 1 for individuals in incubation stage, etc.) among those of sex g^* and in risk group j.

This model assumes that, conditioning on risk groups, individuals choose their partners irrespective of their syphilis statuses. Therefore, the resulting proportion of Primary/Secondary syphilis among contact traced can be very low when using that formula. We introduce a parameter that allows controlling the prevalence of Primary/Secondary among contacts traced from infectious individuals. More precisely, for d=2, we replace $p_{gr}(t)$ in (11)with :

$$p_{gr}(t;\varepsilon) = \frac{I^{gr}(t)}{\varepsilon\left(I^{gr}(t) + R_e^{gr}(t)\right) + (1-\varepsilon)N_{gr(t)}}, \quad (12)$$

where ε is in the range $(0,1)$.

Finally, we take:

$$nc_{gr2}(t;\varepsilon) = min\left(p_{gr}(t;\varepsilon)\sum_{g^*}\sum_j m_{gr,g^*j}(t)\chi_{gr,g^*j}\tilde{p}_{g^*j}N_{gr}(t)\ , nc_{gr}(t)\right) \quad (13)$$

Similarly, we obtained the rate at which individuals with sex g and in the risk group r are traced using the formula:

$$c^{gr}(t) = \sum_{g^*}\sum_j p_{g^*j}(t;\varepsilon)m_{gr,g^*j}(t)\tilde{p}_{g^*j}\chi_{g^*j,gr}(t) \quad (14)$$

Table A2. Yield (i.e. prevalence of Primary/Secondary syphilis) **of contact tracing** & prevalence of syphilis concordance in stable couples from population surveys

Setting	**Definition: Contact having syphilis**	**Outcome**
PNG [100]	VDRL ≥1:8	In 2,230 contacts traced, overall prevalence **8.8%,** of whom 90 male, 106 female and 1 Transgender infected contact. Gradient of yield/prevalence by number of partners reported by index: 8.05% yield among contacts of index patients reporting 1 partner in last 3 months, 9.9% for those with 2 partners, 7.2% for those with 3-5 partners, and 22.7% for those with >5 partners
North Carolina, USA 2015 [101]	Clinical + RPR (and TPHA?)	Of 2,181 contacts of 1,646 early syphilis cases (of which 65% Primary/ Secondary, and 35% early latent), 241 **(11%)** new diagnoses of which **57% primary/secondary**
Washington state USA, 2010-14 [102]	Not reported	193+162 = 355 contacts syphilis-infected **(28%),** out of 786+463 = 1,249 contacts tested, for being contacts of 'early syphilis' patients
Young MSM, Milwaukee, 2011-12 [103]	Not reported	55 Facebook-type contacts of 17 index cases with 'newly identified syphilis';17 **(50%)** of 34 tested were syphilis-infected
San Francisco, 2004-08 [104]	Sero-reactive & recently infected based on clinical history & evaluation	1,340 new/early syphilis indexes (303 primary, 567 secondary, 470 early latent; 97% male, 94% gay) reported a total 1,665 contacts (average 1.2 per person), of whom 702 (44%) treated prophylactically (partner not tested or not sero-reactive but exposed during critical period (3m primary + 6m secondary + 12m early latent; this would cover incubation-stage contacts!); 188 (11%) already treated for this syphilis exposure, 125 **(7.5%) sero-reactive and treated for new** syphilis infection.
Louisiana USA, 1993-96 [105]	Disease staging (no details)	12,927 patients (45% male; 1,782 primary, 3,765 secondary & 7,360 early latent; of themselves 3,245 identified through partner notification; named 29,248 (mean 2.3) contacts, of whom 22,825 examined and 9,374 (**41%**) infected. Of the infected contacts, 57% had already received treatment and 43% were newly identified contacts. 66% of contacts were located within 21d of index patient's interview., which for 52% of indexes was on the day of assignment to a DIS i.e. treatment. Total average delay to newly identified contacts median 22-90 days.
Montgomery county, Alabama, USA, 1991, 21-week campaign during epidemic of early syphilis [106]	Not reported in abstract	373 index patients had partner notification investigations; 113 **(11%)** of 984 sex partners and 41 (3%) of 1,146 high-risk associates (persons identified during cluster investigations) had syphilis
Florida & New Jersey, USA, 1999-3 [107]		1,966 index patients (9% primary, 18% secondary, 73% early latent), randomized to 3 partner notification approaches, gave 2,236 partners located, of whom 1,732 examined of whom 406 previously treated, another 367 **(21%) infected** & 870 of those testing negative received preventive treatment.
India national, Centre for Global Health Research health check-up, 2006 [108]	TPHA	Of 19 syphilis-infected (identified by screening, i.e. not only Primary/ Secondary stage cases) married couples 3 **(16%) were concordant-positive**, in 4 (21%) only the woman was positive, and in 12 (63%) only the man positive.

Annex 3. Prevalence data, (a) PNG and (b) Peru*:*
XLS available from Avenir Health

References for PNG: [40-45, 77, 85, 94, 109-124].
References for Peru: [33, 36, 54, 73, 82, 117, 125-151].

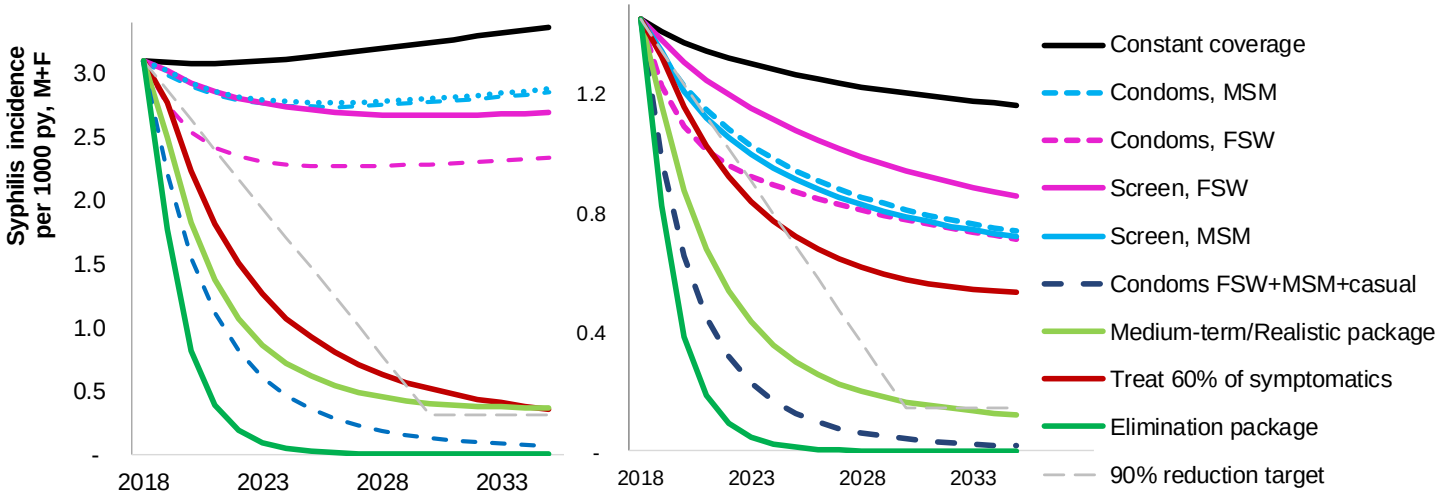
Annex 4. Sensitivity analyses: parametrizations and detailed results

Annex 4a. First sensitivity analysis: Alternative natural history calibration

An alternative natural history calibration assumed lower rates of incidental cure, expressed as a longer average duration of Latent syphilis, absent program-based treatment, of 40 years, instead of the default 15 years, in line with WHO global estimates [7, 29, 30] and the example South Africa STI model [19].

In this alternative calibration, the baseline (default) incidence rates were 20% lower in both countries, even though the projected prevalence, fitted to surveillance data, did not change. The higher incidence rates resulted in stronger impacts toward elimination for any intervention (Figure A4a).

Figure A4a. Prevention, screening and treatment scenarios, in a calibration with 40 years instead of 15 years average duration of latent syphilis: (a) PNG; (b) Peru



Annex 4b. Second sensitivity analysis: Alternative, less assortative mixing between groups

The main advantage of the default mixing structure (Annex 1) is that the parameters that mixing is parameterized by the proportions married for each risk group, which can directly be obtained from national household surveys, like Demographic and Health Surveys, and key population surveys like Integrated Biological and Behavioural Surveys. However, this formulation does not allow partnerships between medium- and high-risk heterosexuals. This may lead to over-estimating the chances and ease of eliminating an STI – which is a serious concern for this model set-up to inform syphilis *elimination* strategies.

We considered an alternate mixing formulation for sensitivity analysis, that allowed mixing between medium-risk and high-risk groups. This alternate formulation uses a weighted combination of proportionate and assortative mixing in medium-risk and high-risk groups, with mixing coefficients specified as follows:

$$\tilde{q}_{g,r,g^*,j}(t) = \frac{z_{g,r}(t)-q_{g,r}(t)}{z_{g,r}(t)}\left[(1-\xi)\frac{\left(z_{g^*,j}(t)-q_{g^*j}(t)\right)N_{g^*,j}(t)}{\sum_{k\in[\text{medium,high}]}\left(z_{g^*,k}(t)-q_{g^*,k}(t)\right)N_{g^*,k}(t)}+\xi\delta_{r,j}\right] \quad (15)$$

In this equation, $z_{g,r}-q_{g,r}$ is the average number of non-marital partnerships members of this group form per year. The term $\delta_{r,j}$ is the Kronecker delta ($\delta_{r,j}=1$ if $r=j$ and $\delta_{r,j}=0$ otherwise). The parameter $0\leq\xi\leq 1$ controls the extent of assortative mixing in the medium-risk and high-risk groups, such that when $\xi=1$, all non-marital partners of high-risk individuals are from the high-risk group as in the default mixing structure, while when $\xi=0$, the numbers of partnerships that (e.g.) high-risk women prefer with medium-risk and high-risk men are proportional to the number of partnerships supplied by each group. This formulation entails a trade-off: if high-risk individuals draw more partners from the medium-risk group, they draw fewer from the high-risk group and vice-versa.

The effect of the more proportionate mixing on syphilis transmission is a reduction in the overall force of infection. To maintain epidemic fit to prevalence data, we compensated this by specifying higher partner change rates (Table A4b). Of note, the much increased partner change rates needed in this calibration, notably for medium-risk women, suggest that this mixing matrix is less realistic.

In this alternative calibration, the ranking of impacts across interventions was largely maintained, except that interventions targeting FSW – especially condoms – became more impactful (due to an increased numbers of such high-risk contacts), notably in comparison to clinical treatment as a stand-alone intervention which is not targeting these higher-risk contacts (Figure A4b).

Figure A4b. Impact projections for a subset of key interventions in calibrations with mixing added between medium-risk and high-risk groups

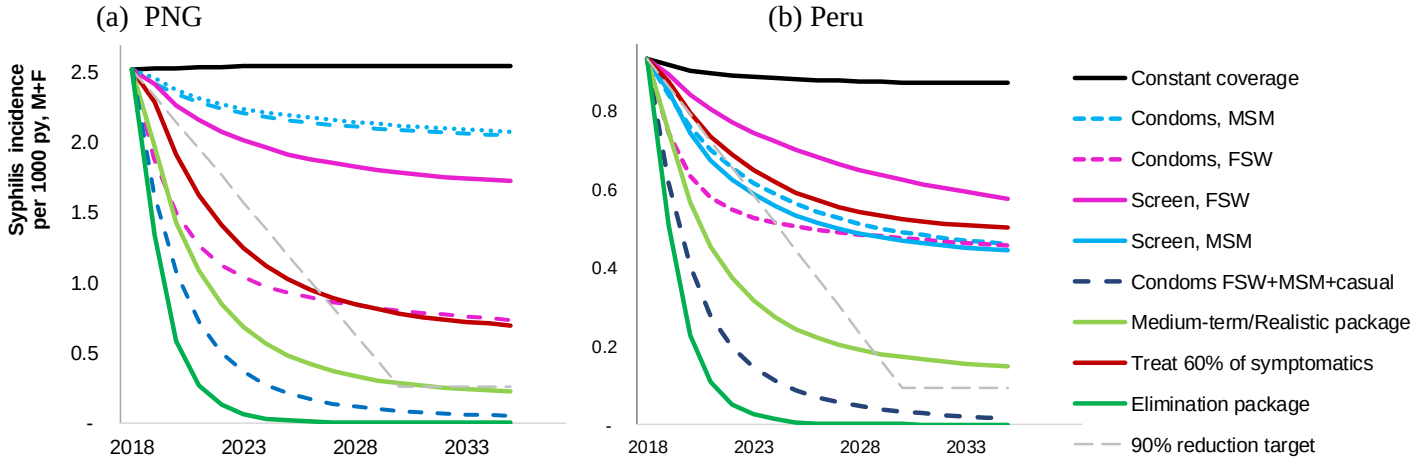


Table A4b. Parametrization of a calibration with mixing added between medium-risk and high-risk heterosexuals

	PNG	Peru

Proportion of high-risk contacts with high-risk population	**Default**		**+ MR/HR mixing**		**Default**		**+ MR/HR mixing**	
	100%		**0%**		**100%**		**0%**	
	Input	Output	Input	Output	Input	Output	Input	Output
Partners per medium-risk man per year	3	3.5	5.7	6.2	3	3.6	5	5.8
Partners per medium-risk woman per year	3	2.9	5.7	**57**	3	2.9	5	**54**
Partners per high-risk man per year	5	5.4	11	11.4	5	5.4	13	12
Partners per FSW per year	55	54	110	**60**	55	54	120	**57**

Note to Table A4b. The outputted partner change rates differ from those user-inputted rates, as a result of the model's balancing between supply and demand for partners across the groups (see Annex 1). This became a large adjustment in the current sensitivity analysis, as adding mixing between medium-risk with high-risk groups un-balanced the inputted partner change rates.

Annex 4c. Larger high-risk male population

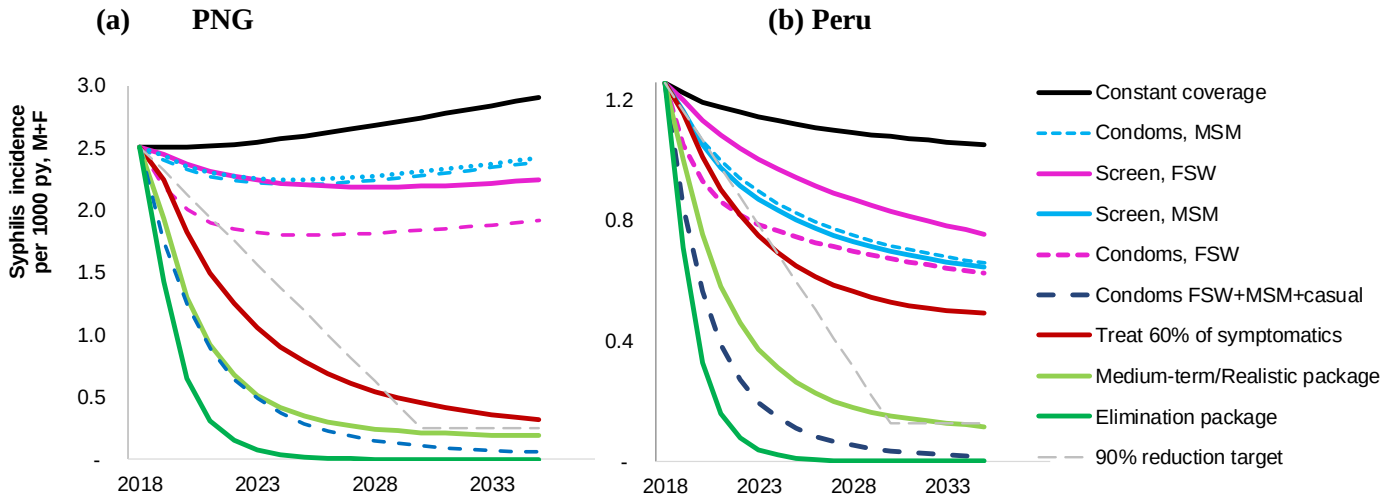
As an alternative approximation of having more higher-risk men mixing with the lower-risk population, we explored a calibration with larger population of higher-risk men, and smaller population of medium-risk men. The larger number of higher-risk men was compensated by a lower number of high-risk (FSW) contacts per man per year (Table A4c), such that baseline prevalence fit was maintained.

This calibration resulted in broadly similar ranking of interventions and intervention packages (Figure A4c), compared to the default (Figure A4c). Due to the larger high-risk male (FSW client) population, relative impact increased slightly for interventions and packages targeting FSW (condoms and screening) while it decreased for less FSW-targeted interventions, viz. clinical treatment of symptomatic primary/secondary cases across all groups, and the 'medium' package with moderate coverages of all interventions.

Table A4c. Parametrization of a calibration with larger group of high-risk men

	PNG		**Peru**	
	Default	**More high-risk**	**Default**	**More high-risk**
High-risk men population size	16%	28%	9%	18%
Medium-risk population size	28%	16%	28%	19%
Partners per high-risk man per year	5	4	5	4
Partners per FSW per year	55	65	55	65

Figure A4c. Impact projections for a subset of key interventions in calibrations with a larger high-risk male population: (a) PNG, (b) Peru



Annex 4d. Individual-based simulation of exposure and new infections to low-risk adults.
XLS available from Avenir Health

Note to Annex 4d:
A final, fourth sensitivity analysis examined how the default mixing structure may over-estimate risk and prevalence in low-risk heterosexual groups, resulting from the model's compartmental structure by which low-risk individuals effectively have a different (marital) partner annually.

In a stand-alone simulation, risk and resulting prevalence to low-risk people was simulated on an individual basis, in the extreme case of having one unique partner throughout the simulation, over a period of 10 years.

This simulation gave 0.83-fold to 0.85-fold lower prevalence at its 10-years end-point, compared to the default model, within a range of initial low-risk prevalences of 0.05-3.0%.

This illustrates that our compartmental model, by ignoring the real pair-based risk structure for low-risk people, slightly over-estimates (=country-level incidence: the bias at national level would be:

- 4-8% share of low-risk groups in country-wide incidence (Table 3 in the main report);
- multiplied with 15-17% over-estimated syphilis rates in that group (= 1 minus the 0.83-to 0.85-fold prevalence ratio, individual-based simulation versus compartmental model).

This minor change in the incidence and incidence share if low-risk groups is estimated to not make any material difference to patterns of intervention (cost-)effectiveness and ranking.

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