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Strategies for elimination of syphilis in Peru –
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SUMMARY

Background: Control of syphilis is a key component of Peru's national HIV/STI control strategy and activities. We applied a compartmental dynamical model of adult syphilis transmission to examine possible future program scale-up scenarios and inform national STI control strategy and targets.

Methods: The model was calibrated to national data on syphilis prevalence, adult and congenital syphilis case notifications, risk behaviours, intervention coverage, test and condom procurement and distribution volumes and service delivery costs, from routine surveillance, surveys, research studies and program records. Scenarios examined the impact of different combinations of clinical treatment of symptomatic, infectious early-stage cases, contact tracing, syphilis screening and condom promotion, in one or more high-risk or lower-risk groups on syphilis infections averted, cost and cost per infection averted over 2021-2030. Coverage targets were set by STI experts from Peru during online consultation.

Results: The model's calibration highlight the significant impact that Peru's HIV/STI program has had on syphilis transmission between 2000-2019. The decline is particularly marked in FSW and their clients, and reflects increased usage of condoms and the roll-out of periodic screening. In contrast, syphilis rates in MSM and bisexual men have remained high. MSM appear to be under-recognized in syphilis notifications, and have become an increasingly important contributor to or even driver of overall syphilis endemicity. Comparing model outputs and case notification rates it appears that a substantial number of adult and congenital syphilis cases remain under-reported and probably un-diagnosed and untreated, although reporting completeness improved considerably from 2015 to 2019.

Of the different interventions evaluated, improving contact tracing, clinical treatment coverage, and condom usage and screening of MSM were projected to have the most impact and best cost-effectiveness.

Conclusions: Peru's STI prevention efforts have helped to reduce the prevalence and incidence of syphilis in adults. In order to eliminate syphilis, Peru will need to scale-up contact tracing as an essential component of clinical STI treatment services and expand condom promotion and screening services,

especially for MSM. Further integration of syphilis testing and condom promotion with other Ministry of Health programs could contribute to increased efficiency and impact.

Abbreviations:
ANC = antenatal care; FSW = Female Sex Worker; (I)BBS = (Integrated) Bio-Behavioural Survey; DHS = Demographic and Health Survey; MSM = Men who have sex with men; 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.

INTRODUCTION

Control of syphilis is a key component of Peru's national HIV/STI control strategy and activities. According to WHO estimates, compared to other countries in the Americas region, Peru has a relatively low prevalence of syphilis in pregnant women, and this fell from 2012 to 2016 – whereas the America regional prevalence increased [1].

Peru's National HIV/STI strategy and multi-sectorial health plan have targets for controlling STIs, including among key populations, men who have sex with men (MSM) and transgender women. A National 2017-2021 Plan commits the country to eliminate congenital syphilis by 2021 [2].

Recent HIV/ STI program developments include the use of rapid syphilis tests, in both health services and mobile/outreach services, since 2010 [3] and rapid dual HIV/syphilis tests since 2017-2018, strengthening laboratory capacity and networks, strengthening STI case reporting, combination HIV/STI prevention including peer education, distribution of condoms and lubricants, decentralization of treatment to the first level of care, and differentiated strategies for key populations including pre-exposure prophylaxis (PrEP) in some high-HIV regions.

Syphilis Interventions Towards Transmission (SITE) is a newly tool developed by Avenir Health with support from the World Health Organization's regional office for the Americas (PAHO). This model simulates adult syphilis transmission in a country and can be used to look at the impact and cost-effectiveness of different STI control programs and interventions, guiding countries toward syphilis elimination target [4]. The model was piloted in Peru to identify opportunities for optimizing STI and syphilis control strategy, plan, targets and cost estimates.

The piloting of SITE took place between June and September 2020 and involved Peru's ministry of health, HIV/STI program, PAHO/WHO regional and country offices and Avenir Health who together calibrated the model, reviewed national data inputs and developed relevant program scenarios. This report presents a compilation of syphilis epidemiological and programmatic data, the model calibration based on those, and projection results for several alternative program scenarios suggested as relevant by the national HIV/STI program. We present and discuss results in terms of the health and transmission impact, service levels and cost of the alternative and combined packages of prevention, screening and treatment interventions.

METHODS

Model: structure and population group sizes

Syphilis Interventions Towards Elimination (SITE) is compartmental dynamic model [4]. The model divides the adult (15-49 years) population into 7 groups based on sexual risk behaviours [4] (Table 1). In addition, there are two groups of not yet sexually active women and men. The software, written as an add-on package in R, version 4.0.2 [5], and instructions and training materials for users, are freely available https://avenirhealth.org/software-site.php .

Natural history

The SITE model distinguishes six infection stages (Annex 1). Susceptible individuals acquire infection at a rate 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. If untreated, infected individuals move sequentially from incubation stage to primary/ secondary syphilis and then latent syphilis. Primary and secondary syphilis are combined, as the diagnostic tests used for screening do not distinguish between these stages and evidence regarding differential infectivity is limited.

Rates of movement between stages reflect average stage duration (Annex 1) and treatment coverage. Individuals in latent stage, in addition to symptom-driven treatment and screening-based treatment, may get cured inadvertently when treated for other infections with an antibiotic effective against syphilis. All treated individuals become susceptible to reinfection at the same rate as those who have never been infected.

Only individuals with primary/secondary infection are assumed to be infectious. Transmission is modelled via probabilities per sex act and fitted, within plausible ranges (Annex 1), to reproduce country prevalence data (Annex 2).

Interventions

The model is structured to simulate four types of interventions:

- **Screening followed by treatment:** based on screening with a treponemal (TPHA or TPPA-based) test followed by confirmation with a Rapid Plasma Reagin (RPR) test. When detected as positive, the consequent treatment effect was modelled as follows:
    - Primary/Secondary infection: 40% become RPR-negative and susceptible to reinfection immediately; the remainder become temporarily immune to reinfection, remaining RPR-positive during that period;
    - Latent stage: 100% are temporarily RPR-positive and immune to reinfection;
    - Recovered but not yet susceptible: 100% get diagnosed and treated again, but they remain in the same infection stage, without change to its remaining duration [6, 7].

- **Clinical treatment, following care seeking for symptoms during primary/secondary infection:** 60% of individuals in the primary/secondary stage are assumed to be symptomatic, throughout all years and scenarios. Of those symptomatic primary/secondary-stage patients who get treated effectively, 40% become RPR-negative and susceptible to reinfection immediately [7]; the remaining 60% also recover and become non-infectious, but remain temporarily RPR-positive and immune to reinfection.

  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 [7, 8].

- **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 Female Sex Workers (FSW) and their clients do not refer each other. Prevalence among contacts is calculated dynamically, assuming that most contacts tested would most typically have been infected by the index case (and not the other way around) – considering the types of partners referred, 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 type of partner referred.

- **Condom usage:** Modelled as an average protective coverage, randomly distributed within a population group and type of partnership [4], which lowers the probability of transmission per-act by 80%.

Model parameterization for Peru

National population sizes were taken from the 2019 World Population Prospects, 2015-2020 estimates and 2015-2030 projections in the medium (i.e. intermediate-growth) variant [9].

In SITE (and in this report) the term MSM also includes bisexual men. For the Peru simulations we have assumed that 25% of MSM have a stable female (e.g. marital) partner.

Risk group sizes and behavioural parameter values (including condom usage) were fitted to surveillance data, data from surveys including Integrated Bio-Behavioural Surveys (IBBS), study and program data (Table 1 & Annex 2) and the values for the same parameters in the Spectrum-Goals [10] model as calibrated in two independent studies looking at Peru's national HIV epidemic [11, 12] and an HIV 'Modes of Transmission' analysis conducted for 2010 [13].

Estimates of the coverage of each of the 4 interventions in 1990 and 2019/20 are shown in Table 2. The Table also details the data and assumption underlying each of these. In brief:

- Syphilis screening: For FSW and MSM based on IBBS data with program-recorded HIV testing coverage as upper limit [14]; for low- and medium-risk women based on routine ANC program data; the overall total screening volumes, including the modelled groups without specific coverage data, were triangulated with test procurement and distribution/usage volumes, from routine program records for the year 2019.
- Clinical treatment: The coverage of clinical treatment was based on national case notifications, which include individuals with confirmed active syphilis (defined as dual positivity on a rapid (TPHA-based) and an RPR test with titer ≥1:8 [15]) and probable active syphilis (defined as positivity on a rapid TPHA-based test). We focused on case notifications from 2019, the most recent data available, and the year with the most complete case reports. In 2015 Peru adopted a new national norm for STI case notification and case notifications have been increasing since then [15].
    - For MSM and FSW/TG women, the sum of modelled diagnoses from screening and clinical symptom-driven treatment, were in line with syphilis diagnoses self-reported by these groups in a 2019 survey [16, 17].
- Contact tracing: Coverage in 2020 was assumed to be 0%. Under the norm 4c, since the 1990s, Peru implements contact tracing and presumptive treatment (without serological testing) of all partners of syphilis patients. Over 2016-2018, the reported number of presumptive treatments of contacts each year totalled 11-21% of that year's number of reported active syphilis cases. It is not known, however, how many of those partners actually had syphilis, i.e. the yield of the contact tracing. For simplicity, the coverage was assumed to be 0% in the current model calibration, but a higher coverage could be proposed for a next updated calibration.

Prevalence data used for model calibration

National and subnational syphilis prevalence data were compiled from a PubMed search, government reports, other published reviews and local experts (Annex 2). To be eligible, samples needed to be collected from 1988 or later, sample size of 25 or greater and based on an internationally recognised diagnostic test with adequate performance characteristics.

For low-risk and medium-risk women, prevalence data were from sentinel surveys over 1988 to 2010 and routine program screening data over 2008-2019 on pregnant women visiting Ante-Natal Care (ANC) [18].

For men, Peru had prevalence data from community surveys. In addition, 5 surveys were identified conducted in indigenous communities [19-22]. Indigenous people in the Amazonian region (estimated in 2017 to cover 0.8% of Peru's population [23]) are known to have higher HIV and STI risks and rates, in part due to lower health care access [19-21]. In the model calibration, these data were treated as medium-risk (male and female) groups.

To complement these data, additionally we considered prevalence among blood donors screened. Blood bank screening data were available over 2011-2017. For syphilis, these screening results were not disaggregated by sex, but since the majority of blood donations are typically from men (although no specific data were available) we considered the syphilis screening results to be representative of men in the general heterosexual population.

The projection for FSW and MSM was fitted to sentinel surveillance, IBBS and other published surveys (Annex 2). In addition, since representative survey data were limited for the period after 2011, we considered program and clinic data for these groups [24, 25], although these were of less certain representativity for the overall populations of FSW and MSM. The calibration for MSM additionally considered surveys among Transgender women, another high-risk group that in some surveys and studies was pooled together with MSM (Annex 2). Since its population size is not well-known in Peru, in the SITE model Transgender women were considered to be part of the MSM group.

Before fitting the model to these prevalence data, the prevalence 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 [26-28]. These adjustors do not take into account RPR titers. For those studies that defined syphilis as TPHA positive and RPR positive above a threshold titer of ≥1:8 (and one FSW study with RPR ≥1:4), the observed prevalence was increased 2.5-fold. This multiplier is based on comparative prevalence from studies in Peru of dual positivity with and without RPR titers (Annex 3 [16, 29-37]).

Estimating Maternal and Congenital syphilis cases, 2015-2019

The SITE-modelled prevalence estimates for low-risk and medium-risk women was combined with program-reported ANC-1 attendance, ANC-based syphilis screening and ANC-based syphilis treatment coverage (Annex 2), to estimate congenital syphilis (CS) cases. This estimation used the same method as the WHO global and regional congenital syphilis case estimations, which distinguishes between Adverse Birth Outcomes (clinical symptomatic congenital syphilis in a liveborn infant, miscarriage, stillbirth and prematurity/Low-Birth Weight) alongside non-symptomatic congenital syphilis cases (i.e. any other birth to a syphilis-infected mother who was not adequately treated for syphilis during the pregnancy) [1]. Results were compared with national case notifications of maternal and congenital syphilis, for the period 2015-2019, the years after a new national directive for improved syphilis case notification was adopted [15, 38].

Intervention scenarios and impact assessment

Three different syphilis program scenarios combining the 4 different types of interventions were simulated over 2021-2030 (Table 2):

1. Constant coverage, as at 2019-2020;
2. Scale-up variant 'Moderate': gradual increase to target coverages, starting in 2021 and reached by 2023, and maintained thereafter;
3. Scale-up variant 'Maximum': gradual increase to target coverages, starting in 2021 and reached by 2023, and maintained thereafter.

As additional scenarios, we scaled up one intervention at a time (screening, or clinical treatment, or condom promotion) for one or more risk groups (FSW, or MSM, or condom promotion specific to people with casual partnerships) to illustrate patterns of impact and cost-effectiveness.

Cost and cost-effectiveness

Intervention scenarios were costed by applying service delivery unit costs (per test, treatment, condom, or contact traced) to volumes of services. Cost-effectiveness was assessed as cost (in US$) per syphilis infection averted, over 2021-2030. No discounting was applied to cost or infections. Cost data were based on national HIV/STI program data if available, or alternatively from costing data from other countries (in the region) or global estimates (see footnotes to Table 4).

RESULTS

Epidemic calibration: Prevalence trend, 1988 to 2019

Figure 1 shows the diagnostic test adjusted prevalence data in the 7 model populations and the results from the model calibrated to these data. In all 7 groups, the modelled prevalence fell over time (Figure 1).

The model results are in keeping with the historic declines in HIV in FSW and MSM linked to increased condom use [11, 12, 31] (Figure 1c). For MSM the model was calibrated to a more moderate prevalence decline than might be suggested upon first looking at the data. This is because the comparability of the MSM data points is not clear, as they come from different sites and use different sampling methods, including program data over 2012-2019. For example, early studies (e.g. [39]) may well have over-sampled higher-risk MSM [13].

In the model declines in the prevalence of syphilis in FSW and MSM drive parallel declines in the prevalence in the other (lower-risk) male and female groups. It should be noted, however, that Peru's ANC data did not indicate any clear trend, nor did the male data.

Epidemic calibration: Incidence, 1998 to 2019

Data on the incidence of syphilis are limited. Three studies were founds:

- MSM: A study in Lima reported an incidence of syphilis of 84 per 1000 person-years in 1998-2000 [40]; in comparison, the model projected an incidence among MSM of 28/1000 person-years in 1999.
- High-risk heterosexual men and women:
  - a 1-year cohort study in low-income neighbourhoods of 3 cities in 2003 measured a post-screening incidence of 44/1000 [8]; in comparison, the model projected incidence estimates in 2003 were 16/1000 and 3.2/1000 for high-risk heterosexual women and men, respectively.
  - In the same or similar low-income neighbourhoods, incidence over 2 years (between 2002-2005) after a baseline screening and treatment, was 99/1000 in men who ever had sex with men, and 16/1000 in other high-risk men [41]. In comparison, modelled incidence rates over

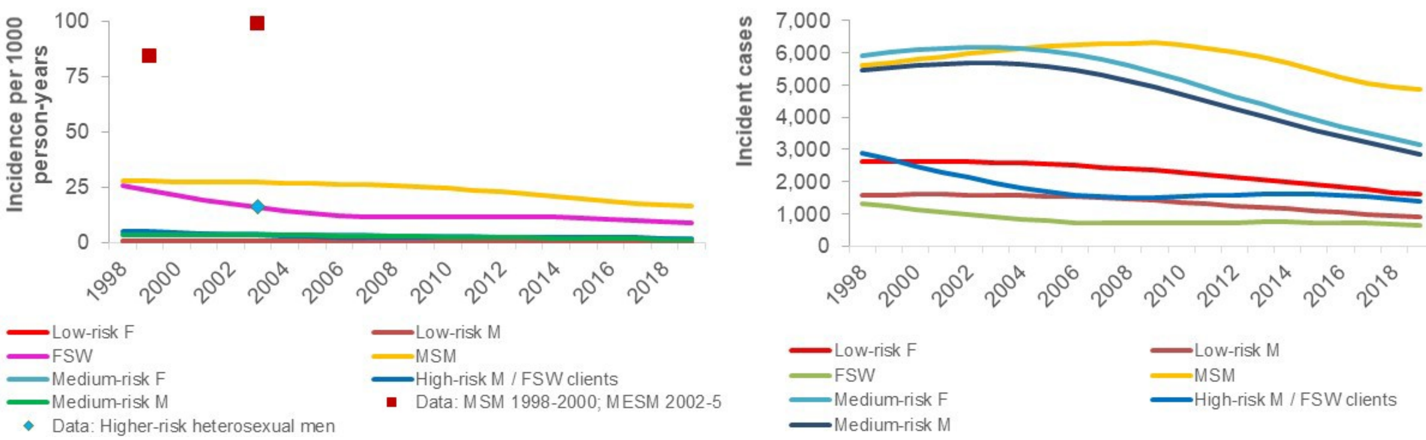
2002-05 averaged 27/1000 and 3.1/1000 for MSM and high-risk heterosexual men, respectively.

The high incidence of syphilis in MSM is also supported by a high proportion of clinic-diagnosed cases in MSM that are primary/secondary phase, and a relatively low coverage of recent RPR tests self-reported by MSM, compared to FSW and TG, at four clinics in Lima [25].

In the model calibration, MSM was the group with the highest incidence rates. The modelled rates (Figure 2a), however, were lower than the values reported in the three studies for MSM and other high-risk men. This difference may be explained by:

1) Studies having selectively sampled higher-risk populations and hence not representative of the whole population;
2) Two of the 3 studies report incidence rates after a mass screening and treatment [8, 41], which may have increased the incidence rate above that typical for the group under non-study conditions by making the entire group including those at highest-risk of infection susceptible to reinfection.

Figure 2. Modelled and observed syphilis incidence, Peru
(a) incidence rate per 1000 uninfected adults; (b) incident cases



Population distribution of incident and prevalent syphilis cases, 2019
In the model calibration, MSM was the group with highest prevalence and incident case number (Figures 1c and 2b) in 2019. In terms of absolute numbers of new cases, medium-risk men and women also contributed considerably to the national total, due to their moderately high prevalence and large group size (Figure 2b).

In 2019, MSM accounted for 49% of male and 32% of overall (male + female) incident cases, although they only represent 3.9% of adult men, making them an important target group for syphilis interventions. The overall prevalence estimated in 2019 was 1.0% in men and 0.50% in women, due to the large contributions of MSM and (secondarily) FSW clients with high prevalence to overall male prevalence. This male-to-female prevalence ratio is higher than the 1.0 ratio found in a national survey in Peru in 2000 [42]. This difference mostly reflects the drop in syphilis rates among FSW [25] and their clients [43] since 2000 following the roll-out of monthly health check-ups required to maintain a sex worker license,

which include STI testing. It may also reflect the model's inclusion of Transgender women with MSM, rather than with women – whereas in the 2000 survey Transgender women may have been counted with women. However, as transgender women are a very small group (quantified at 0.2% of the 15-49-year-old national population, in Peru's national Spectrum-AIM HIV estimation of May 2020 (based on data from Ecuador)[44] this effect will be small.

Epidemic calibration: Diagnosed/notified/treated cases, and tests procured and distributed 2019

Since 2015 Peru implements etiologic STI case management [15], whereas earlier STI case management was mostly syndromic [45, 46]. In 2015 the country also adopted a new norm for STI case notification. These developments have been accompanied by an increase in etiologically syphilis confirmed case notifications.

Peru has three different systems that provide syphilis case notifications: stratified by risk group, by ethnicity or just by sex. The inclusivity or exclusivity between the three systems was not entirely clear, nor was it clear if notifications include cases identified through screening, or mainly cases diagnosed through clinical services. The ethnicity reporting system provided the largest annual case numbers over 2016-2019: for example, 12,381 cases of active syphilis in 2019 (Table 3). In comparison, the model 6,940 women and 7,455 men were treated for syphilis in 2019, following clinic visit for symptoms or diagnosis through screening – which is consistent with the notifications (Table 3).

Program notifications include more female than male cases, in part due to a considerable volume of maternal cases reported through the ANC/PMTCT screening program [47]. In contrast, the model included a slightly larger volumes of cases among MSM and men overall, due to a larger number of clinical (symptom-driven) treatments.

The modelled number of screenings of ≈970,000 in 2019 is consistent with numbers of test kits nationally procured and purportedly used in 2019, i.e. the modelled screenings were within the range of the program-reported rapid tests (used for screening) and the program-reported sum of TPHA, RPR and FTA-ABS (used for confirmatory testing), shown in Table 3 as green-shaded cells. This comparison provides some indication of the consistency of modelled and actual screening volumes, however with some uncertainties:

- The procurement and distribution data do not tell which tests types were used for screening, and which for confirmation, and how many of persons positive on a screening test received a confirmatory test. With test algorithms varying across sites and service points, the data do not provide a direct indication of numbers of persons screened and diagnosed;
- Program-reported test volumes assume that each kit or unit was used at its full capacity (e.g. a rapid test kit for 25 assessments);
- Some populations and persons receive multiple tests within 1 year, for example, the norm in Peru is to screen pregnant women twice in a pregnancy, to screen FSW and MSM twice per year, and to screen transgender women four times per year, although the implementation of these norms varies. This may explain why the program recorded 1.42 million persons screened, whereas the model estimated just below 970,000.

Table 3. Program-reported and modelled screening volumes and syphilis cases diagnosed during clinical treatment and screening; program-reported screening tests distributed, Peru 2019

2019	Program, syphilis case notifications				Modelled diagnoses, from screening and clinical treatments		
	F	M	F or M	F + M	F	M	F + M
Women (non-maternal/non-ANC)	1,390				1,984		
Maternal / ANC	2,259				3,058		
Men		2,712				3,010	
Adolescents			751				
MSM		1,432				3,364	
Transgender women	95						
Sex worker (F or M)	524				773		
Andean				89			
Indigenous Amazonian				884			
Mestizo				11,293			
Ethnicity unspecified				115			
Total	**4,268**	**4,144**	**751**	**12,381**	**5,815**	**6,374**	**12,189**
Diagnoses from clinical treatment					729	1,660	**2,390**
Diagnoses from screening					5,086	4,713	**9,799**
Persons screened				**1,421,115**	795,415	171,359	**966,774**
Rapid screening tests procured & distributed				**3,003,500**			
TPHA, RPR and FTA-ABS tests procured and distributed				**403,500**			

Note to Table 3. Routine case notifications came from 3 different data systems, by sex (excluding ANC), by risk group or by ethnicity; without precise information on the overlap between the systems. The total was largest (12,381) for the recordings by ethnicity.

Epidemic calibration: Maternal and congenital syphilis cases, 2012-2019

The modelled and reported numbers of maternal cases were in line for years 2018-2019 (Figure 1d). The model-estimated case reporting completeness (defined as reported cases, relative to estimated cases) in 2019 was 63% for maternal syphilis and 74% for CS (including both ABOs and asymptomatic CS cases). Prior to 2019 both the number of reported maternal and reported congenital cases were much smaller, probably reflecting less complete notification.

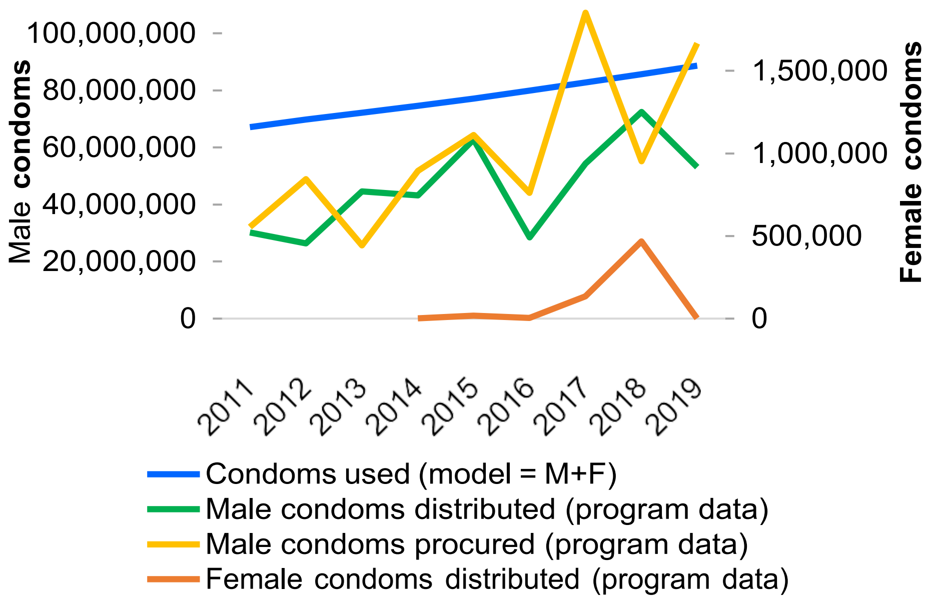
The number of cases of CS in the SITE model calibration fell from 2,997 in 2012 to 605 in 2019. This marked decline reflects a decline in maternal prevalence (Figure 1a), an increase in the coverage of ANC-based syphilis screening (from 74% in 2012 to 95% by 2019) and an increase in the proportion of mothers found syphilis-infected during ANC-based screening who were adequately treated (from 68% in 2012 to 94% by 2019). In 2019, model-estimated CS case incidence rate was 95/100,000 births– about double the WHO's threshold for elimination of 50/100,000.

Epidemic calibration: Condoms distributed, 2011-2019

Modelled numbers of condoms used were in the range of volumes of condoms reported by the program as procured and distributed (Figure 3). The modelled increase over 2011-2019 in condoms used is in line

with program-reported increases in procurement and distribution. A slightly higher number used than procured and distributed by the public HIV/STI program could reflect condoms bought privately.

Figure 3. Program-reported numbers of condoms procured and distributed, in comparison to modelled condoms used



Notes to Figure 3. The comparison does not account for an up to 15% typical condom wastage rate. Program-reported condom volumes fluctuated somewhat over the years, which could reflect reporting inaccuracy or delay, or a delay from procurement to distribution.

Projected interventions impact: 2021-2030

Figure 4 shows the change in syphilis incidence between 2021 and 2030, in response to the three intervention packages and to a coverage increase in each of the interventions individually. Of the individual interventions, clinical treatment of symptomatic Primary/Secondary cases had the largest impact (Figure 4). Enhancing treatment coverage to 50% of symptomatic, infectious cases, above Peru's moderately low current treatment coverage, reduced incidence in 2030 by 62%.

Contact tracing, even without improving treatment seeking and coverage by symptomatic self-referring patients, by itself had an impact reducing incidence in 2020 by 17%. This reflects that contact tracing effectively reaches many early-stage and so infectious cases (Figure 4): in the model calibration for Peru, across the 7 risk groups between 3-63% of contacts traced, and an overall average of 34%, had active syphilis.

Scaling-up periodic syphilis screening was most effective when targeted to MSM, a group with high prevalence and low current screening coverage. In contrast, screening low- and medium-risk women only had little impact (Table 3), due to their very low prevalence.

Increasing condom use in FSW from 45% to 65% and, in particular, in use by MSM contacts (40% to 60%) lowered syphilis incidence in 2030, relative to the Constant coverage scenario, by 14% and 50% respectively, and was thus more powerful than increasing screening coverage.

Further scale-up of condom usage and syphilis screening in FSW had an impact similar to that of screening or condom usage among low- and medium-risk women. This is because by 2019-2020, condom use and screening coverage were already high among FSW and consequently incidence and prevalence was already quite low in FSW.

Cost & Cost-effectiveness

The overall cost of syphilis prevention, screening and treatment at current coverage levels for the period 2021-2030 was projected to be US$ 64 million when the full cost of condoms was included (Table 3). Sharing condoms costs with the HIV/AIDS program (and/or Maternal and neonatal/child health programs), with the syphilis programme being responsible for 20% of the costs reduced the cost of the 'Constant coverage' intervention package to US$ 30 million.

Of the individual interventions, clinical treatment of symptomatic cases had the lowest cost-per-infection-averted and over 2021-2030 was cost-saving, as the decrease in falling incidence reduced ongoing treatment costs. Contact tracing had a negligible cost-per-infection averted (<US$ 0.01), as it effectively identifies and treats infectious patients.

Condom promotion for MSM and screening of MSM had the next lowest cost-per-infection-averted – for condom promotion, especially so when considering cost-sharing with HIV/AIDS prevention efforts.

Condom promotion and screening for FSW had higher cost-per-infection-averted than for MSM, but still was more cost-effective than condom promotion for casual, medium-risk contacts and screening of low- and medium-risk women.

While syphilis screening – if well-targeted – has a low cost per infection averted, its investment cost may be prohibitively high. For 2019 Peru's total HIV/TB/STI budget and spending were US$ 189.5 million and US$ 188.5 million, respectively; and for HIV/STI without TB US$ 72 million and US$ 71 million, respectively [48]. Annual screening of 50% of FSW and 35% of MSM would add US$ 0.3 million and US$ 1.8 million annually, and screening of lower-risk women as much as US$ 19 million annually.

Cost-per-infection-averted for the two multi-intervention packages were within the range of the individual interventions.

DISCUSSION

Peru was the first country in Latin America to use SITE and the second country in the world. The model, calibrated to Peru, highlights the significant impact that Peru's HIV/STI program has had on syphilis transmission between 2000-2019. The decline is particularly marked in FSW and also in FSW clients i.e. high-risk men, and reflects increased usage of condoms and the roll-out of periodic (up to monthly) health check-ups for FSW that include STI testing [25, 43, 46]. Additionally, the common practice of 3-dose treatment for syphilis with benzathine-penicillin at weekly intervals [25] according to the national guideline for treatment for key populations [49](whereas for lower-risk populations the guideline is 1 single dose of 2.4 million units)[50]) may act as temporary (several weeks) prophylaxis, which for high-risk individuals may be non-negligible.

In contrast, syphilis rates in MSM and bisexual men have remained high and therefore become an increasingly important contribution and driver of overall syphilis endemicity.

Comparison of model results with case notifications suggest that, while reporting completeness improved considerably from 2015 to 2019, a substantial number of adult and congenital syphilis cases remain under-reported and possibly un-diagnosed and untreated. Notably, the modelled share of MSM in total adult syphilis cases (e.g. 4,875 of 15,388, i.e. 49%) is several-fold larger than what routine notifications suggest (1,482 or 12% of 12,381 in 2019). This could reflect that MSM are not being reached with screening and treatment services and that some MSM reached are being classified as heterosexual men.

Continuing with the current interventions at 2018/19 levels, the SITE projections suggest that in 2030 the prevalence of syphilis would be 0.70% in adult men and 0.27% in adult women, and there will be around 450 CS cases yearly. Against this counterfactual, the other modelled scenarios illustrate the potential impact that expanding current interventions or introducing new interventions (e.g. contact tracing) could have on syphilis and identify opportunities for optimizing the ongoing response.

Among biomedical interventions, those targeting primary and secondary syphilis (e.g., enhancing community awareness for symptoms and access to services, thus improving symptom-driven clinical treatment, and contact tracing) are the most impactful and cost-effective for reducing adult transmission – as these specifically target the symptomatic, infectious stage of infection, thus suppressing the transmission cycle.

Screening is effective and cost-effective mainly if targeting high-risk groups, especially MSM, FSW and their clients [51-53] to reduce or eliminate syphilis in the adult and overall population. Meanwhile, screening and treatment among pregnant women is the mainstay for eliminating congenital syphilis. Peru's roll-out of rapid point-of-care syphilis tests in 2010 and dual HIV/syphilis tests in 2017-2018 in routine ANC screening [35, 54], and the planned roll-out of dual tests from 2021 across all groups and testing channels [3] is thus pertinent.

As is well known, condoms (or other primary risk reduction interventions) are also highly effective and cost-effective in reducing syphilis transmission, if adopted by at-risk people with consistency. Integrating syphilis testing and condom promotion with other MoH programs could contribute to increased, high efficiency and impact across STI and other basic health programs.

Limitations

As for any model, the validity and accuracy of predictions are limited by uncertainties in model parameters, model structure, and country-specific input data.

In SITE each of the 7 sexually active population groups is assumed to be homogenous, with STI exposure and access to screening and treatment distributed equally. This is a simplification; for example, FSW and MSM and bisexual men often feature strong gradients of risk and service uptake, and some subgroups within these populations are systematically un-reachable and may not even be identified as part of the group. For example, clandestine FSW in Lima had much higher syphilis prevalence [55]than FSW seen in program services and clinics, or in sentinel surveillance (Annex 2). The greater the heterogeneity, the harder it is to eliminate an infection [52], meaning that SITE may be over-optimistic regarding the impact of interventions targeting known key population groups.

Limiting the model to 7 distinct groups also means that some populations are not explicitly modeled (e.g. Transgender women, cross-dressers/transvestites, prisoners and injecting drug users). Surveys have shown these to be at high risk of syphilis; however they constitute a small (though not well quantified) part of the national population [13, 17, 35, 56-59] and were implicitly captured within the modelled FSW, MSM/bisexual men, FSW clients and medium-risk groups.

Peru furthermore features marked variations in HIV and STI rates and risks geographically with higher risk and rates in the capital and in the Selva regions. The current analysis did not look at geographical differences; a future application of the SITE model could look at tailoring the calibration and program target scenarios to each region's specific situation and needs [60-62].

At the cross-section between model and data, SITE is being calibrated on prevalence data, but underlying incidence remains uncertain. In the model, for a given prevalence the underlying incidence varies with rates of treatment (clinic-based and following screening) and of incidental cure from latent syphilis. As a result, incidence levels and rates, and the absolute number of infections that simulated program scenarios could avert, remain inevitably uncertain. Still, uncertainty in incidence rates should not invalidate the presented patterns of impact and cost-effectiveness across alternative intervention types and target groups (which are also broadly similar to two earlier modelled settings [4]).

On the cost side, unit costs assumed for the respective interventions were based on global data. Country-specific budget and spending data including indirect service delivery costs (that include health worker time, infrastructure, program management) remain pending, and may change patterns of cost-per-infection-averted. The cost-effectiveness took the narrow perspective of eliminating adult syphilis transmission and infections, and thus ignored external additional benefits, such as for maternal and new-born health (through ANC screening), family planning and prevention of other STIs (through condoms); the presented results cannot therefore by themselves drive strategy, policy and allocation decisions.

Recommendations for surveillance

As a limitation in country data, for FSW Peru's latest national survey was from 2006 [63]; therefore we had to rely on program clinic data (Annex 2 and Figure 1c) to calibrate current prevalence. Furthermore, for FSW as well as MSM (and Transgender women) prevalence observed in surveys (surveillance surveys and IBBS) was typically much above that measured in routine program screening data (Figure 1c). This difference, also found in STI data from other countries around the world [64], probably reflects that people accessing routine services are those who have benefited more from prevention and are generally of lower-risk. It leaves considerable uncertainty on current syphilis in these key groups, and consequently on the expected impact and cost-effectiveness of prioritizing them above other populations. Notably for Transgender women, with prevalence across the (few) programmatic and survey data points ranging wide, improved surveillance is key.

Among non-key populations, adults indigenous communities had markedly higher prevalence than other non-key population men and women; this is another group to intensify surveillance for.

Conclusion

Peru's STI prevention, care and treatment efforts have played a role in preventing and controlling syphilis in the population. In order to eliminate syphilis, scaling up clinical STI treatment at primary level, contact tracing, condom promotion and screening services, especially for MSM, bisexual men and Transgender women will be essential.

Table 1. Population sub-group sizes and their sexual behaviour characteristics in the SITE model calibration of Peru

Group (15-49 years)	Population share	People, 2019	Married / with stable hetero-sexual partner	Partners /year	Sex acts/ partner /year	Source*
Not yet Sexually Active Women	14%	1,180,922	NA	0	NA	DHS [60-62]
Low-Risk Women	55%	5,072,062	100%	1	75	DHS [60-62], community surveys [65, 66] including among indigenous populations [22], ANC surveys [67] and model's balancing of stable & casual partnerships between women and men
Medium-Risk Women	39%	2,108,790	30%	2.5 casual partners	35	
High-Risk Women/FSW	0.87%	73,386	12%	75 clients	3.3	National size estimations; HIV/STI sentinel surveillance surveys 2002-2011; studies [55, 68-71]. FSW career duration of 8 years, based on [69-71]
All Women	**100%**	**8,435,160**				2019 World Population Prospects [9]
Not yet Sexually Active Men	9.5%	821,112	NA	0	NA	DHS [60-62]; [72]
Low-Risk Men	53%	4,546,365	100%	1	90	Fitted, balancing behaviours reported in community surveys [43, 60-62, 65, 66, 73-75], including among indigenous populations [22] and PREVEN ([46, 63]) and balancing with FSW/client group size and numbers of FSW/client contacts
Medium-Risk Men	25%	2,160,820	40%	2.5 casual partners	35	
High-Risk Men	9.0%	777,895	30%	5 FSW	3.3	
MSM & bisexual men	3.9%	337,088	25% (i.e. bisexual)	4.3	12	National size estimations, HIV/STI sentinel surveillance surveys 2002-2019 [16, 30 , 31, 42, 57], other surveys and studies [30-32, 72, 76, 77]
All men	**100%**	**8,643,280**				2019 World Population Prospects [9]

Notes to Table 1. * Additional to the specific stated sources, all parameters were informed by their corresponding value in a national HIV Modes of Transmission analysis conducted for the year 2010 [13] and two independent Spectrum-Goals model representations of Peru's national HIV epidemic [11, 12].

Table 2. Syphilis intervention coverage: historic, current and for alternative program target scenarios scaling-up one or several interventions at a time

Population group	Historic	Current & Constant-coverage, 2019-2020	Single-intervention scale-up, 2023+	Scale-up: Moderate	Scale-up: Maximum	Source or estimation method for historic & current coverage
	1990			2023+, all interventions combined		
Clinical treatment of symptomatic Primary/ Secondary episodes						
Low- & Medium-risk Women	25%		50% across all groups	40% across all groups	50% across all groups	5% medical treatment of all active/recent syphilis; 28-50% of females/males/MSM used medicine for self-reported GUD [73]; among MSM patients, 33% non-adherent and not completing the recommended 3 doses of penicillin on time [36]
High-risk women = FSW	35%					
Heterosexual men	32%					
MSM	32%					
Contact tracing: contacts traced per symptomatic index case treated						
All groups	0		0.40	0.20	0.40	Program and study data from other countries [4]; contact tracing from ANC women foreseen in 2021 plan & budget [3]
Screening coverage, per year						
Low- & Medium-risk Women	0	11%	25%	15%	20%	HMIS, HIV/STI and ANC program statistics over 2014-2019 combined with 2014 DHS [62] for ANC-1 coverage [78]; for 2021, as of January 2020 Peru envisioned increasing annual tests used in the ANC context (ANC women, their partners and infants) by 25% [3]
High-risk women = FSW	16%	30%	50%	35%	45%	59% of FSW and 42% of MSM attending 4 key population clinics in Lima reported having RPR-tested in 2 years prior [25]; program statistics [14, 46]; national HIV/STI program testing data and diagnoses (Table 3); self-reported syphilis diagnoses in MSM and TG women [16, 17]; screenings in Low/Medium-risk men may be blood donors, reactive and referred for confirmatory testing & treatment in HIV/STI services. All groups combined: fitted to 2019 program-reported syphilis test procurements and distributions (Table 3); targets reflect the plan to roll-out rapid dual HIV/syphilis tests to all populations (beyond ANC) from 2021 [3].
Low-risk Men	0	0	NA	5%	5%	
Medium-risk Men	0	5%	NA	5%	10%	
High-risk Men = FSW clients	0	5%	NA	5%	10%	
MSM	0	7.5%	35%	20%	30%	
Condom use: sex acts protected						
Medium-risk / casual	1%	14%	25%	20%	25%	DHS [60-62], sentinel surveillance and other surveys (see Table 1)
High-risk (FSW/client)	22%	45%	65%	55%	65%	
MSM	21%	40%	60%	50%	60%	

Notes to Table 2: Targets were agreed in August 2020, taking into account challenges, falling budget and changed health sector priorities post-COVID.

Table 4. Cost and cost-effectiveness of syphilis control and elimination scenarios, 2021-2030, Peru

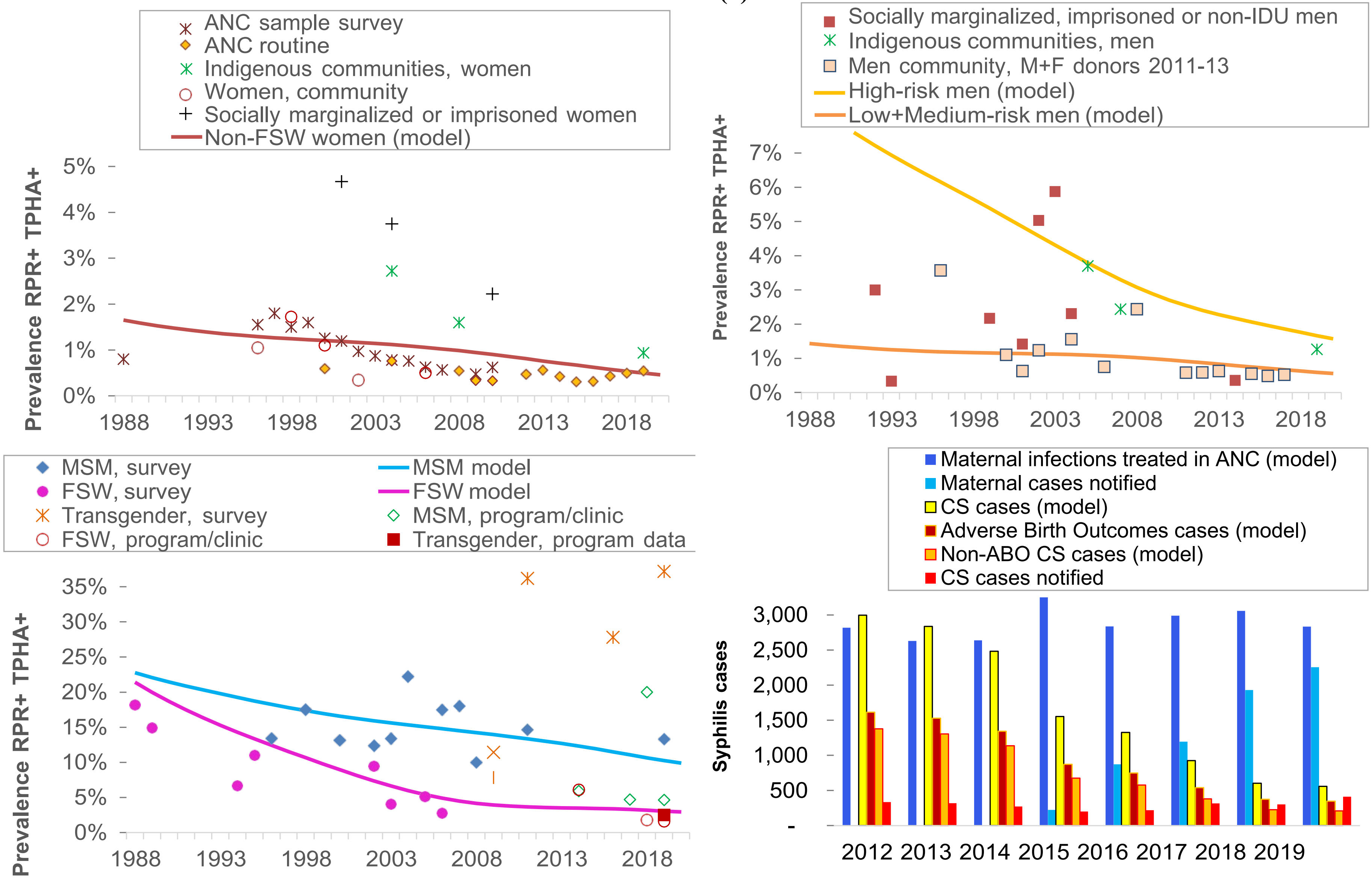
Service delivery volumes, 2021-2030:	Screening		Treatments		Contacts traced & diagnosed		Cost (screening + treatment + condoms), 2021-2030		Infections averted, 2021-2030	Incidence rate at 2030, relative to Constant Coverage	Cost per infection averted	
	Screenings	Contacts traced	Index patient	Positives on screening		Condoms used	Condoms, full cost	Condoms, 20% shared cost			Condoms, full cost	Condoms 20% shared cost
Constant, at 2019-2020 coverages	10,138,609	-	20,214	74,717	-	454,421,052	$ 64,286,769	$ 29,920,725	-			
Screen, Low+Medium-risk Women	19,530,810	-	18,995	94,785	-	454,421,052	$ 83,748,885	$ 49,382,841	2,691,987	11%	$ 7.2	$ 7.2
Screen, FSW	10,274,109	-	19,700	75,467	-	454,421,052	$ 64,566,388	$ 30,200,344	1,147,119	5%	$ 0.24	$ 0.24
Screen, MSM	11,002,486	-	16,715	109,001	-	454,421,052	$ 66,177,356	$ 31,811,312	7,471,929	30%	$ 0.25	$ 0.25
Contact tracing	10,138,609	13,849	18,090	67,756	3,068	454,421,052	$ 64,294,246	$ 29,928,202	4,407,123	17%	$ 0.0017	$ 0.0017
Clinical treatment, symptomatic cases	10,138,609	-	20,244	65,380	-	454,421,052	$ 64,252,393	$ 29,886,348	15,132,500	62%	$ (0.0023)	$ (0.0023)
Condoms, FSW/client	10,138,609	-	18,248	71,101	-	488,950,412	$ 69,096,167	$ 30,862,834	4,317,249	14%	$ 1.11	$ 0.22
Condoms, MSM	10,138,609	-	14,646	67,562	-	487,541,923	$ 68,865,117	$ 30,789,535	13,120,130	50%	$ 0.35	$ 0.07
Condoms, Medium-risk/casual contacts	10,138,609	-	18,904	72,880	-	650,736,033	$ 78,014,468	$ 32,654,784	3,365,496	13%	$ 4.08	$ 0.81
Program scale-up package: Moderate	16,423,072	4,334	13,218	92,492	592	592,011,562	$ 89,297,923	$ 45,335,002	21,737,208	82%	$ 1.15	$ 0.71
Program scale-up package: Maximum	20,174,150	5,832	10,360	95,718	621	718,311,562	$ 108,249,140	$ 55,320,998	28,658,647	96%	$ 1.53	$ 0.89

Notes to Table 4. Unit costs assumed for scenario costing and cost-effectiveness analysis:

- 1 adult screened: **US$ 2.1** across possible screening algorithms in ANC clinics in Peru [79], in line with a global congenital syphilis investment case analysis [80].
- 1 adult with confirmed syphilis treated for syphilis (with 3 doses of benzathine penicillin; labor and supplies & counseling): **US$ 5.8,** built up of US$ 3.7 for treatment + counselling & US$ 2.1 for testing prior to treatment [11, 79-81].
- 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$ 0.14** for FSW and MSM, based on the Avenir Health regional estimate for Latin America of US$ 0.22-0.35 [82]; US**$ 0.07** for medium-risk beneficiaries with casual partnerships. In comparison, Peru's national procurement cost were US$0.03 and $0.77 per male and female condom, respectively; excluding distribution and overhead.

Figure 1. Model calibration to national syphilis prevalence and case report data, Peru, 1988-2019:
(a) Low- and medium-risk women; (b) Heterosexual men; (c) FSW and MSM; (d) pregnant women in ANC and congenital syphilis.

(a) **(b)**



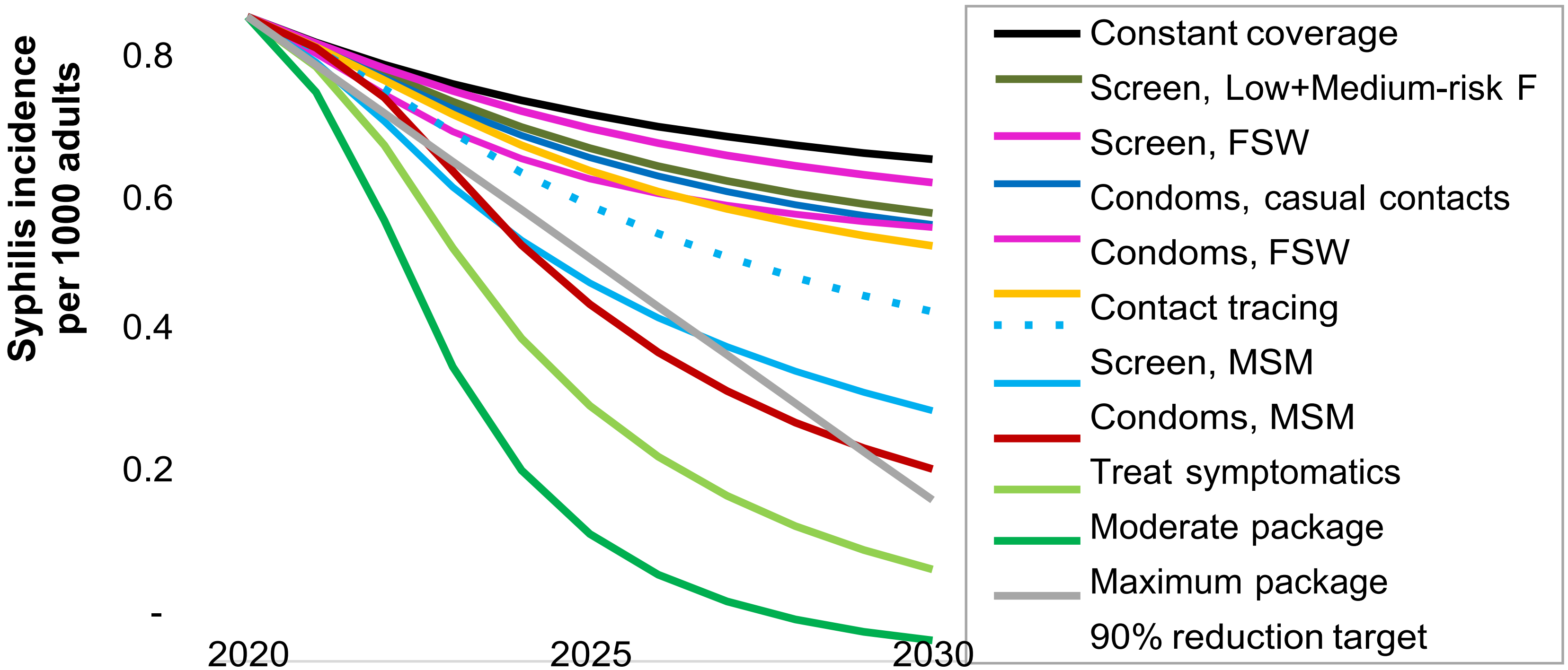
(c) **(d)**

Notes to Figure 1. Prevalence data show after adjustment for diagnostic test performance (see Methods).

In Panel (c), not shown is a 51% prevalence among 45 MSM who cross-dressed, in 1996 [30]. Data are shown for transgender women (male-to-female), which in the model are not distinguished as a separate group but rather to be thought of as a sub-group of MSM - in line with several studies and surveys that also pooled MSM with transgender women.

In panel (d), the Congenital Syphilis (CS) cases estimated by the model (yellow bars) is the total of Adverse Birth Outcomes (ABO) cases (red bars) + Non-ABO CS cases (orange bars). Peru's national CS case definition includes all births (liveborn, stillborn and abortion) to mothers with untreated or inadequately treated confirmed active syphilis [38], in line with the WHO surveillance case definition.

Figure 4. Model projections of Syphilis incidence rates in Peru (2019 to 2030) under alternative prevention, screening and treatment scenarios



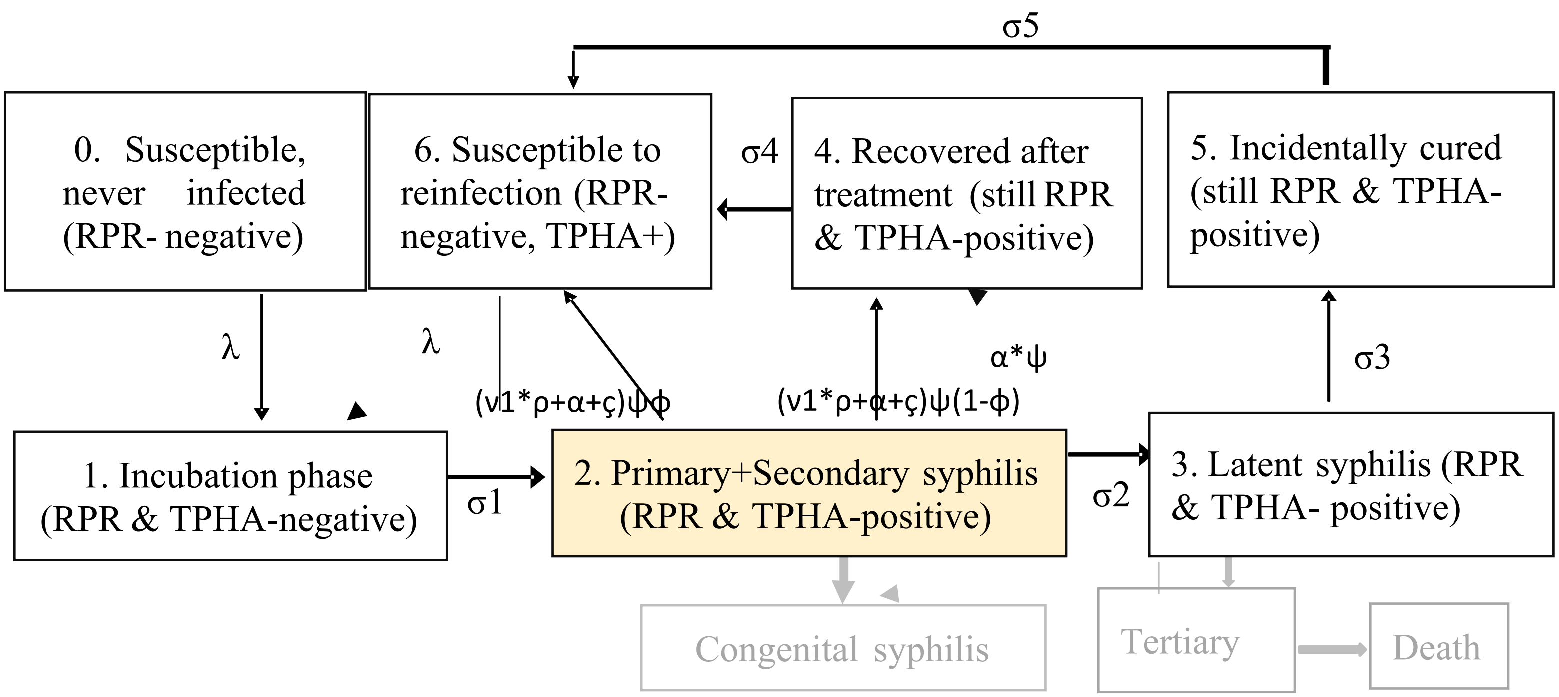
Notes to Figure 4: The '90% reduction target' (dashed grey line) shows a hypothetical reduction of 90% in the incidence rate by 2030 from 2020, which could be considered as an operational goal for syphilis elimination as a public health problem, in line with the impact target of the WHO global health sector strategy for STI control, 2016-2021, of a 90% syphilis incidence reduction from 2018 to 2030 [83].

Annex 1. SITE model biomedical parameters used in the Peru calibration

The Syphilis Interventions Towards Elimination (SITE) model is described in detail in [4].
The software and user guides are available at: https://avenirhealth.org/software-site.php

Figure S1 shows the natural history representation of syphilis in SITE.
Table S1 details the parameters that determines transitions between infection stages, and their values in the Peru calibration.

Figure S1.



Notes to Figure 1: Reproduced from [4].
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 [84]. 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 [1].

Table S1. Biomedical parameters, and their values in the SITE model's calibration to Peru

Parameter (compartment of natural history flow chart)	**Symbol in equations**	**Value & unit**	**Uncertainty range**	**Source & comments**
Duration of infection:				South Africa model [7] and WHO global estimates [26-28]
Incubation (1)	1/σ1	4 weeks	2-6	
Primary + secondary stage, untreated (2)	1/σ2	28 weeks	18-78	Longer than the commonly assumed 18-26 weeks [6, 7, 85-89], as SITE 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/σ3	520 weeks = 10 years	260-1,560	Incidental cure, from exposure to oral penicillin, tetracyclines like doxycycline, macrolides like azithromycin or other antibiotics taken for skin, respiratory and other non-STI-infections [90, 91] 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 [92]. We assumed latent syphilis, when not detected and treated following programmatic screening, to last 10 years, similar to assumptions in the WHO global STI estimates [26-28] and a syphilis transmission model for South Africa [7]
Recovered after treatment (4)	1/σ4	26 weeks	3-260	[7]
Incidentally cured (5)	1/σ5	130 weeks	3-260	[7]
Susceptible to reinfection (6)	Λ	Dynamic result		Dynamic calculation of the Force of infection see [4]
Treatment of Primary/secondary cases:				
Primary/Secondary cases that are symptomatic	P	60%	40-85%	[7, 26-28]
Probability of cure when treated, after clinic attendance for symptoms of Primary/Secondary infection	Ψ	80%	54%-95%	54-93% in Peru [8, 36] and considering (1) lower effectiveness of single-dose treatment against latent syphilis; (2) a 'yo-yo' effect of people getting re-infected soon by their (stable) partners, absent contact referral (e.g. [8]; (3) losses along the diagnosis/treatment cascade including among key population members diagnosed during screening [36].)
Primary + Secondary stage cases who upon treatment turn RPR-seronegative immediately	Φ	40%		[7]
Transmission probabilities per sexual act:				

Parameter (compartment of natural history flow chart)	**Symbol in equations**	**Value & unit**	**Uncertainty range**	**Source & comments**
Woman-to-man		0.04	0.0005-0.20	[7, 93-95], applying during Primary + Secondary stage only
Man-to-woman		0.08	0.0008-0.30	[7, 93-95], applying during Primary + Secondary stage only
MSM		0.10	0.001-0.10	[51, 86-88, 95], applying during Primary + Secondary stage only
Reduction in transmission probability, per act, from condom usage		80%	80-90%	[95-100]. 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, when combined with survey-based condom rates, resulted in unrealistically large syphilis declines.

Annex 2. Peru's syphilis prevalence data, and their mapping to modelled risk groups
XLS
For ANC routine data, Annex 2 (in columns S to AA) furthermore shows the coverage of: having at least 1 ANC visit among pregnancies nation-wide (abbreviated ANC-1 attendance), of syphilis screening among ANC women, and of syphilis treatment among pregnant women diagnosed with active syphilis during ANC. These three service coverage indicators, together with maternal syphilis prevalence, are used to estimate congenital syphilis case incidence ([1] & see Methods).

References: [16, 17, 19-22, 25, 29-32, 34, 39, 42, 43, 55-57, 63, 66, 68, 70-73, 77, 101-116].

Annex 3. Comparative syphilis prevalence with and without RPR titer cut-off, studies from Peru

Before calibrating the SITE model to national prevalence data, the prevalence 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 [26-28]. These adjustors do not take into account RPR titers.

To find an adjustment factor for those studies that defined syphilis as TPHA-positive and RPR-positive above a threshold titer, we analysed comparative syphilis prevalence within and across Peruvian data sets, by diagnostic algorithm, notably those with and without an RPR titer cut-off: [16, 29-37, 39, 66, 117].

Across the data points from any all populations, the average and median ratio in prevalence with, versus without RPR titer cut-off, were 3.9 and 2.5, respectively (Table below). There was no evidence of a larger ratio for a stricter (higher) RPR cut-off (viz. for ≥1:16 versus ≥1:8).

The adjustment factor for studies that defined syphilis as TPHA-positive and RPR-positive above a threshold titer of ≥1:8 (and one FSW study with RPR ≥1:4), was therefore set at a 2.5-fold increase. These ratios are in line with an average ratio of 4.0 found in a similar analysis using surveillance data from Bangladesh [118].

Population	Year	RPR titer	N tested	Observed prevalence: Rapid test alone	RPR alone	TPHA alone	RPR & TPHA	TPHA&RPR >= titer	RPR>= titer	Location	Source	Ratio, with/without RPR tite: 1:8 & 1:16	RPR 1:8	RPR 1:16
FSW	2005	1:8	3,482	2.8%	5.7%		5.1%	0.7%		10 cities	P. Campos, A. Buffardi, *et al.* Sex Transm		7.1	
FSW	2005	1:16	3,482	2.8%	5.7%		5.1%	0.3%		10 cities	Infect, 82 (2006), pp. 22-25	17.8		17.8
Heterosexual	1996	1:16	28				3.6%	-		Lima	Tabet-S *et al.* 2002; Sanchez-J et al. 2007	Infinite		Infinite
Low-income heterosexual women, community	2004	1:8	320				3.8%	2.2%		Lima, Trujillo, and Chiclayo	Snowden-JM, Konda-KM et al. Sex Transm Dis, 37 (2010), pp. 75-80 & Clark-JL et al. PLoS ONE 2009	1.7	1.7	
Low-income heterosexual men, community	2004	1:8	2,424				2.3%	1.4%				1.6	1.6	
Low-income MSM, community	2004	1:8	541				22.2%	10.5%				2.1	2.1	
MSM	1996	1:16	261				13.4%	8.8%		Lima	Tabet-S *et al.* 2002; Sanchez-J et al. 2007	1.5		1.5
MSM	1998	1:16	1,211				17.5%	6.9%		Lima	Sanchez-J et al. J Acquir Immune Defic Syndr, 2007. 44(5): 578-85	2.5		2.5
MSM	2000	1:16	1,357				14.8%	2.9%		Lima		5.1		5.1
MSM	2002	1:16	1,358				12.4%	3.4%		Lima		3.6		3.6
MSM	2003	1:16	3,280				13.4%	3.4%		Lima, Sullana,	Lama-JR, Agurto-HS et al. 2010; Lama-JR e	3.9		3.9
MSM	2006	1:16	2,599				17.5%	7.4%		Arequipa,	National Sentinel Surveillance Round 5	2.4		2.4
MSM including MSW, bisexual & TG	2011	1:16	1,108				20.9%	8.4%		Ica, Sullana,	report 2011; Sanchez-Fernandez-J 2011	2.5		2.5
MSM including MSW, bisexual & TG	2011	1:8	5,101		0.3%		13.8%	5.1%		Guayaquil	Pizzicato-LN et al., 2017	2.7	2.7	
MSM	2019	1:8	1,768	17.7%	15.2%	20.9%	13.3%	4.5%		11 cities	Sánchez-G, Konda-K & Gonzales-P, 2019	3.0	3.0	
High-risk MSM	2013-14	1:16	312				42.0%	16.8%		Lima	Kojima-N et al., BMC-Inf Dis 2017	2.5	2.5	
High-risk TG	2013-14	1:16	89				57.3%	6.7%		Lima	Kojima-N et al., BMC-Inf Dis 2017	8.6	8.6	
MSM & TG	2011	1:8	1,569				20.0%	8.7%		Lima	Tang-EC et al., 2015	2.3		2.3
MSM & TG	2016	1:8	302				27.8%	12.6%		Lima	Allan-Blitz-LT et al., 2019	2.2		2.2
Bisexual	1996	1:16	101				11.9%	2.0%		Lima	Tabet-S, Sanchez-J *et al.* AIDS 2002, 16: 1271-77; Sanchez-J et al. J AIDS 2007, 44(5): 578-85	6.0		6.0
Travestis / Cross-dresser	1996	1:16	48				51.1%	28.9%		Lima		1.8		1.8
Mujeres Trans-Generos	2009	1:8	450		21.6%				5.1%	Lima	Silva-Santisteban-A et al., AIDS Behav 2012			
Mujeres Trans-Generos	2019	1:8	1,198	51.2%	47.8%	58.1%	45.3%	13.3%		11 cities	Sánchez-G, Konda-K & Gonzales-P, 2019	3.4	3.4	
AVERAGE												**3.9**	**3.6**	**4.3**
MEDIAN												**2.5**	**2.7**	**2.5**

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